Essential Organic Chemistry

THIRD EDITION

Paula Yurkanis Bruice

ALWAYS LEARNING

PEARSON

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السلام علیکم ورحمۃ اللہ وبرکاتہ:

معزز ممبران: آپ کا وٹس ایپ گروپ ایڈمن "**اردو بکس**" آپ سے مخاطب ہے۔

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گروپ میں کسی بھی قادیانی، مرزائی، احمدی، گستاخِ رسول، گستاخِ امہات المؤمنین، گستاخِ صحابہ و خلفائے راشدین حضرت ابو بکر صدیق، حضرت عمر فاروق، حضرت عثمان غنی، حضرت علی المرتضیٰ، حضرت حسنین کریمین رضوان اللہ تعالیٰ اجمعین، گستاخ اہلبیت یا ایسے غیر مسلم جو اسلام اور پاکستان کے خلاف پراپیگنڈا میں مصروف ہیں یا ان کے روحانی و ذہنی سپورٹرز کے لئے کوئی گنجائش نہیں ہے لہذا ایسے اشخاص بالکل بھی گروپ جوائن کرنے کی زحمت نہ کریں۔ معلوم ہونے پر فوراً ریموو کر دیا جائے گا۔

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- **لیڈیز کے لئے الگ گروپ کی سہولت موجود ہے جس کے لئے ویریفکیشن ضروری ہے۔**
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اللہ تبارک تعالیٰ ہم سب کا حامی و ناصر ہو

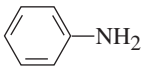
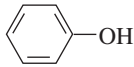
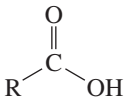
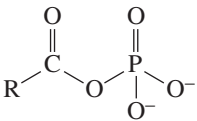
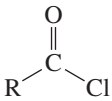
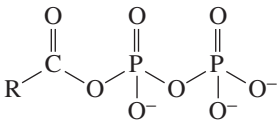
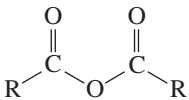
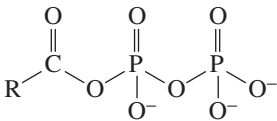
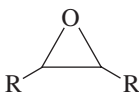
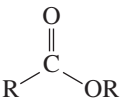
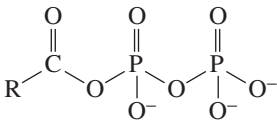
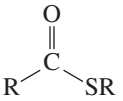
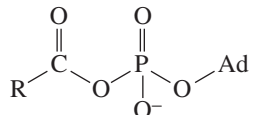
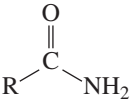
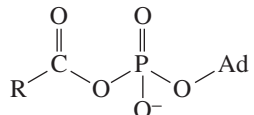
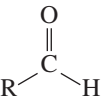
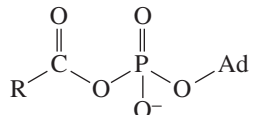
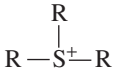
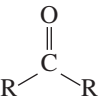
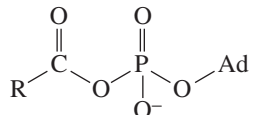
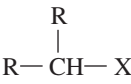
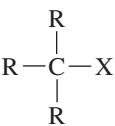
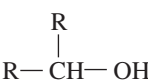
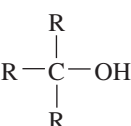
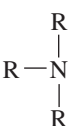
TO THE STUDENT

Welcome to the fascinating world of organic chemistry. You are about to embark on an exciting journey. This book has been written with students like you in mind—those who are encountering the subject for the first time. The book's central goal is to make this journey through organic chemistry both stimulating and enjoyable by helping you understand central principles and asking you to apply them as you progress through the pages. You will be reminded about these principles at frequent intervals in references back to sections you have already mastered.

You should start by familiarizing yourself with the book. Inside the front and back covers is information you may want to refer to often during the course. The list of Some Important Things to Remember and the Reaction Summary at each chapter's end provide helpful checklists of the concepts you should understand after studying the chapter. The Glossary at the end of the book can also be a useful study aid. The molecular models and electrostatic potential maps that you will find throughout the book are provided to give you an appreciation of what molecules look like in three dimensions and to show how charge is distributed within a molecule. Think of the margin notes as the author's opportunity to inject personal reminders of ideas and facts that are important to remember. Be sure to read them.

Work all the problems *within* each chapter. These are drill problems that you will find at the end of each section that allow you to check whether you have mastered the skills and concepts the particular section is teaching before you go on to the next section. Some of these problems are solved for you in the text. Short answers to some of the others—those marked with a diamond—are provided at the end of the book. Do not overlook the "Problem-Solving Strategies" that are also sprinkled throughout the text; they provide practical suggestions on the best way to approach important types of problems.

In addition to the *within-chapter* problems, work as many *end-of-chapter* problems as you can. The more problems you work, the more comfortable you will be with the subject matter and the better prepared you will be for the material in subsequent chapters. Do not let any problem frustrate you. If you cannot figure out the answer in a reasonable amount of time, turn to the *Study Guide and Solutions Manual* to learn how you should have approached the problem. Later on, go back and try to work the problem on your own again. Be sure to visit www.MasteringChemistry.com, where you can explore study tools, including Exercise Sets, an Interactive Molecular Gallery, and Biographical Sketches of historically important chemists, and where you can access content on many important topics.

The most important advice to remember (and follow) in studying organic chemistry is DO NOT FALL BEHIND! The individual steps to learning organic chemistry are quite simple; each by itself is relatively easy to master. But they are numerous, and the subject can quickly become overwhelming if you do not keep up.

Before many of the theories and mechanisms were figured out, organic chemistry was a discipline that could be mastered only through memorization. Fortunately, that is no longer true. You will find many unifying ideas that allow you to use what you have learned in one situation to predict what will happen in other situations. So, as you read the book and study your notes, always make sure that you understand *why* each chemical event or behavior happens. For example, when the reasons behind reactivity are understood, most reactions can be predicted. Approaching the course with the misconception that to succeed you must memorize hundreds of unrelated reactions could be your downfall. There is simply too much material to memorize. Understanding and reasoning, not memorization, provide the necessary foundation on which to lay subsequent learning. Nevertheless, from time to time some memorization will be required: some fundamental rules will have to be memorized, and you will need to learn the common names of a number of organic compounds. But that should not be a problem; after all, your friends have common names that you have been able to learn and remember.

Students who study organic chemistry to gain entrance into professional schools sometimes wonder why these schools pay so much attention to this topic. The importance of organic chemistry is not in the subject matter alone. Mastering organic chemistry requires a thorough understanding of certain fundamental principles and the ability to use those fundamentals to analyze, classify, and predict. Many professions make similar demands.

Good luck in your study. I hope you will enjoy studying organic chemistry and learn to appreciate the logic of this fascinating discipline. If you have any comments about the book or any suggestions for improving it, I would love to hear from you. Remember, positive comments are the most fun, but negative comments are the most useful.

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Common Functional Groups

Name	Structure
Alkane	RCH_3
Alkene	$\diagdown C{=}C \diagup$ (internal); $\diagdown C{=}CH_2$ (terminal)
Alkyne	$RC{\equiv}CR$ (internal); $RC{\equiv}CH$ (terminal)
Nitrile	$RC{\equiv}N$
Ether	$R{-}O{-}R$
Epoxide	three-membered ring with O, R substituents
Thiol	$RCH_2{-}SH$
Sulfide	$R{-}S{-}R$
Disulfide	$R{-}S{-}S{-}R$
Sulfonium ion	$R{-}\overset{+}{S}(R){-}R$
Aniline	$C_6H_5{-}NH_2$
Phenol	$C_6H_5{-}OH$
Carboxylic acid	$R{-}C(=O){-}OH$
Acyl chloride	$R{-}C(=O){-}Cl$
Acid anhydride	$R{-}C(=O){-}O{-}C(=O){-}R$
Ester	$R{-}C(=O){-}OR$
Thioester	$R{-}C(=O){-}SR$
Amide	$R{-}C(=O){-}NH_2$, $\diagdown NHR$, $\diagdown NR_2$
Aldehyde	$R{-}C(=O){-}H$
Ketone	$R{-}C(=O){-}R$
Benzene	C_6H_6 ring
Pyridine	six-membered aromatic ring with N
Acyl phosphate	$R{-}C(=O){-}O{-}P(=O)(O^-){-}O^-$
Acyl pyrophosphate	$R{-}C(=O){-}O{-}P(=O)(O^-){-}O{-}P(=O)(O^-){-}O^-$
Acyl adenylate (Ad = adenosyl)	$R{-}C(=O){-}O{-}P(=O)(O^-){-}O{-}Ad$

	primary	secondary	tertiary
Alkyl halide	$R{-}CH_2{-}X$ X = F, Cl, Br, or I	$R{-}CH(R){-}X$	$R{-}C(R)(R){-}X$
Alcohol	$R{-}CH_2{-}OH$	$R{-}CH(R){-}OH$	$R{-}C(R)(R){-}OH$
Amine	$R{-}NH_2$	$R{-}NH(R)$	$R{-}N(R){-}R$

Approximate pK_a Values

Common Symbols and Abbreviations

[α]	specific rotation
α	observed rotation
Ad	adenosyl
ATP	adenosine triphosphate
B_0	applied magnetic field
Bu	butyl
D	Debye; a measure of dipole moment
δ	partial or chemical shift
Δ	heat
$\Delta G^{\ddagger}$	free energy of activation
ΔG°	Gibbs standard free energy change
ΔH°	change in enthalpy
ΔS°	change in entropy
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
E	entgegen (opposite sides in *E,Z* nomenclature)
E_a	energy of activation
Et	ethyl
Et_2O	diethyl ether
FAD	flavin adenine dinucleotide
H_2CrO_4	chromic acid
HOCl	hypochlorous acid
IR	infrared
k	rate constant
K_a	acid dissociation constant
K_{eq}	equilibrium constant
$LiAlH_4$	lithium aluminum hydride
MS	mass spectroscopy
μ	dipole moment
$NaBH_4$	sodium borohydride
NAD^+	nicotinamide adenine dinucleotide
NaOCl	sodium hypochlorite
nm	nanometers
NMR	nuclear magnetic resonance
pH	measure of the acidity of a solution ($= -\log [H^+]$)
pI	isoelectric point
pK_a	measure of the strength of an acid ($= -\log K_a$)
PLP	pyridoxal phosphate
ppm	parts per million (of the applied field)
R	alkyl group; group derived from a hydrocarbon
R,S	configuration about an asymmetric center
THF	tetrahydrofuran or tetrahydrofolate
TMS	tetramethylsilane, $(CH_3)_4Si$
TPP	thiamine pyrophosphate
UV/Vis	ultraviolet/visible
X	halogen atom
Z	zusammen (same side in *E,Z* nomenclature)

Essential Organic Chemistry

THIRD EDITION

GLOBAL EDITION

Paula Yurkanis Bruice

UNIVERSITY OF CALIFORNIA
SANTA BARBARA

PEARSON

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New chapter on Acid/Base Chemistry reinforces fundamental concepts and foundational skills needed for future topics in organic chemistry.

MasteringChemistry®
for Organic Chemistry

MasteringChemistry tutorials guide you through topics in chemistry with self-paced tutorials that provide individualized coaching. These assignable, in-depth tutorials are designed to coach you with hints and feedback specific to your individual needs. For additional practice on Acids and Bases, go to MasteringChemistry where the following tutorials are available:

- Acids and Bases: Base Strength and the Effect of pH on Structure
- Acids and Bases: Factors that Influence Acid Strength
- Acids and Bases: Predicting the Position of Equilibrium
- Acids and Bases: Definitions

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Preface

In deciding what constitutes "essential" organic chemistry, I asked myself the following question: What do students need to know if they are not planning to be synthetic organic chemists? In other words, what do they need to know for their careers in medicine, dentistry, applied health professions, nutrition, or engineering?

Based on the answers to that question, I made content and organizational choices with the following goals in mind:

- Students should understand how and why organic compounds react the way they do.
- Students should understand that the reactions they learn in the first part of the course are the same as the reactions that occur in biological systems (that is, that occur in cells).
- Students should appreciate the fun and challenge of designing simple syntheses. (This is also a good way to check if they truly understand reactivity.)
- Students should understand how organic chemistry is integral to biology, to medicine, and to their daily lives.
- In order to achieve the above goals, students need to work as many problems as possible.

To counter the impression that the study of organic chemistry consists primarily of memorizing a diverse collection of molecules and reactions, this book is organized around shared features and unifying concepts, emphasizing principles that can be applied again and again. I want students to learn how to apply what they have learned to new settings, reasoning their way to a solution rather than memorizing a multitude of facts.

A new feature, "**Organizing What We Know about the Reactions of Organic Compounds**," lets students see where they have been and where they are going as they proceed through the course, encouraging them to keep in mind the fundamental reason behind the reactions of all organic compounds: *electrophiles react with nucleophiles*.

When students see the first reaction of an organic compound (other than an acid–base reaction), they are told that all organic compounds can be divided into families and all members of a family react in the same way. To make things even easier, each family can be put into one of four groups and all the families in a group react in similar ways.

The book then proceeds with each of the four groups (Group I: compounds with carbon–carbon double and triple bonds; Group II: benzene; Group III: compounds with an electronegative group attached to an sp^3 carbon; and Group IV: carbonyl compounds). When the chemistry of all the members of a particular group has been covered, students see a summary of the characteristic reactions of that group (see pages 276, 360, 508) that they can compare with the summary of the characteristic reactions of the group(s) studied previously.

The **margin notes** throughout the book encapsulate key points that students should remember. (For example, "when an acid is added to a reaction, it protonates the most basic atom in the reactant"; "with bases of the same type, the weaker the base, the better it is as a leaving group"; and stable bases are weak bases".) To simplify mechanistic understanding, common features are pointed out in margin notes (see pages 435, 443, 474, 478).

There are about 140 **application boxes** sprinkled throughout the book. These are designed to show the students the relevance of organic chemistry to medicine (dissolving sutures, mad cow disease, artificial blood, cholesterol and heart disease), to agriculture (acid rain, resisting herbicides, pesticides: natural and synthetic), to nutrition (trans fats, basal metabolic rate, lactose intolerance, omega fatty acids), and to our shared life on this planet (fossil fuels, biodegradable polymers, whales and echolocation).

Success in organic chemistry requires students to work as many problems as possible. Therefore, the book is structured to encourage problem solving. The answers (and explanations, when needed) to all the problems are in the accompanying *Study Guide and Solutions Manual*, which I authored to ensure consistency in language with the text.

New **Tutorials** following relevant chapters give students extra practice so that they can better master important topics: Acids and Bases, Drawing Curved Arrows: Pushing Electrons, and Drawing Resonance Contributors.

The problems within each chapter are primarily drill problems. They appear at the end of each section, so they allow students to test themselves on the material they have just read to see if they are ready to move on to the next section. Selected problems in each chapter are accompanied by worked-out solutions to provide insight into problem-solving techniques. Short answers are provided at the back of the book for problems marked with a diamond to give students immediate feedback concerning their mastery of a skill or concept.

The many **Problem-Solving Strategies** in the book teach students how to approach various kinds of problems. Each Problem-Solving Strategy is followed by an exercise to give the student an opportunity to use the strategy just learned.

The **end-of-chapter problems** vary in difficulty. They begin with drill problems that integrate material from the entire chapter, requiring students to think in terms of all the material in the chapter rather than focusing on individual sections. The problems become more challenging as the student proceeds. The net result for the student is a progressive building of both problem-solving ability and confidence. (I have chosen not to label problems as particularly challenging so as not to intimidate the students before they try to solve the problem.)

Many of the end-of-chapter problems can also be found in MasteringChemistry. Students can master concepts through traditional homework assignments in Mastering that provide hints and answer-specific feedback. Students learn chemistry by practicing chemistry.

Additionally, tutorials in MasteringChemistry, featuring specific wrong-answer feedback, hints, and a wide variety of educationally effective content, guide your students through the course. The hallmark Hints and Feedback offer scaffolded instruction similar to what students would experience in an office hour, allowing them to learn from their mistakes without being given the answer. Organic Chemistry Tutorials in MasteringChemistry pinpoint errors by assessing the logic and accuracy of the student's answers. Individual evaluators written and linked to each problem by organic chemists look at the validity of the student's entry and generate error-specific feedback based on information received from a JChem database.

The book contains **two new chapters**: "Radicals" and "Synthetic Polymers." There is no longer a chapter on the "Organic Chemistry of Drugs." Much of the material that was in that chapter is now in application boxes, so students have the opportunity to learn about that material who may have not had that opportunity if that last chapter were not covered in their course.

Similarly, some of the information on the chemistry of living systems has been integrated into earlier chapters. As examples, noncovalent interactions in biological systems has been added to Chapter 3, the discussion of catalysis in Chapter 5 now includes a discussion of enzymatic catalysis, and acetal formation by glucose has been added to Chapter 12.

The six chapters (Chapters 16–21) that focus primarily on the organic chemistry of living systems have been rewritten to emphasize the connection between the organic reactions that occur in the laboratory and those that occur in cells. Each organic reaction that occurs in a cell is explicitly compared to the organic reaction with which the student is already familiar. Chapter 18 can be found on the Instructor Resource Center.

The chapter on spectroscopy is modular, so it can be covered at any time during the course—at the very beginning, at the very end, somewhere in between, or not covered at all. When I wrote that chapter, I did not want students to be overwhelmed by a topic they may never revisit in their lives, but I did want them to enjoy being able to interpret relatively simple spectra. In addition to the spectroscopy problems in the text, there are over forty new spectroscopy problems in the *Study Guide and Solutions Manual* with worked-out answers. The answers come after the problems, so students have the opportunity to try to solve them on their own first.

New **modern design, streamlined narrative**, and **bulleted summaries** at the end of each chapter allow students to navigate through the content and study more efficiently with the next.

ACKNOWLEDGMENTS

It gives me great pleasure to acknowledge the dedicated efforts of Jordan Fantini and Malcolm Forbes, who checked every inch of the book for accuracy; David Yerzley, M.D., for his assistance with the section on MRI; Warren Hehre of Wavefunction, Inc., and Alan Shusterman of Reed College for their advice on the electrostatic potential maps that appear in the book; and Jeremy Davis, who created the art that appears on page 147. I am also very grateful to my students, who pointed out sections that needed clarification, worked the problems and suggested new ones, and searched for errors.

The following reviewers have played an enormously important role in the development of this book.

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Second Edition Accuracy Reviewer

Malcolm Forbes, *University of North Carolina*

I am deeply grateful to my editor, Jeanne Zalesky, whose talents guided this book and caused it to be as good as it could be, and to Coleen Morrison, whose gentle prodding and attention to detail made the book actually happen. I also want to thank the other talented and dedicated people at Pearson whose contributions made this book a reality. And thank you to Lauren Layn, the creative brains behind the technology that accompanies the book.

I particularly want to thank the many wonderful and talented students I have had over the years, who taught me how to be a teacher. And I want to thank my children, from whom I may have learned the most.

To make this textbook as user friendly as possible, I would appreciate any comments that will help me achieve this goal in future editions. If you find sections that could be clarified or expanded, or examples that could be added, please let me know. Finally, this edition has been painstakingly combed for typographical errors. Any that remain are my responsibility; if you find any, please send me a quick e-mail so that they can be corrected in future printings of this edition.

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About the Author

Paula Bruice with Zeus, Bacchus, and Abigail

Paula Yurkanis Bruice was raised primarily in Massachusetts. After graduating from the Girls' Latin School in Boston, she earned an A.B. from Mount Holyoke College and a Ph.D. in chemistry from the University of Virginia. She then received an NIH postdoctoral fellowship for study in the Department of Biochemistry at the University of Virginia Medical School and held a postdoctoral appointment in the Department of Pharmacology at the Yale School of Medicine.

Paula has been a member of the faculty at the University of California, Santa Barbara since 1972, where she has received the Associated Students Teacher of the Year Award, the Academic Senate Distinguished Teaching Award, two Mortar Board Professor of the Year Awards, and the UCSB Alumni Association Teaching Award. Her research interests center on the mechanism and catalysis of organic reactions, particularly those of biological significance. Paula has a daughter and a son who are physicians and a son who is a lawyer. Her main hobbies are reading suspense novels, any biographies, and enjoying her pets (three dogs, two cats, and two parrots).

Essential Skills for Organic Chemistry

New features and major revisions to this third edition focus on developing students' problem solving and analytical reasoning skills. Organized around mechanistic similarities, Bruice encourages students to be mindful of the fundamental reasoning behind the reactions of all organic compounds: electrophiles react with nucleophiles.

New Tutorials Skill Builders following select chapters deepen student understanding of key topics while developing their problem solving skills. Tutorials include acid-base chemistry, building molecular models, and drawing curved arrows and are paired with assignable MasteringChemistry® tutorials with wrong answer-specific feedback and coaching.

ACIDS AND BASES

TUTORIAL

Enhanced by MasteringChemistry®

This tutorial is designed to give you practice solving problems based on some of the concepts you learned in Chapter 2. Most of the concepts are given here without explanation because full explanations can be found in Chapter 2.

An Acid and Its Conjugate Base

An acid is a species that can lose a proton (the Brønsted–Lowry definition). When an acid loses a proton (H^+), it forms its conjugate base. When the proton comes off the acid, the conjugate base retains the electron pair that attached the proton to the acid.

CH_3COOH (acid) → CH_3COO^- (conjugate base) + H^+ (a proton)

Often, the lone pairs and bonding electrons are not shown.

CH_3COOH (acid) → CH_3COO^- (conjugate base) + H^+

$CH_3\overset{+}{O}H_2$ (acid) → CH_3OH (conjugate base) + H^+

Notice that a neutral acid forms a negatively charged conjugate base, whereas a positively charged acid forms a neutral conjugate base. (In each case, the charge *decreases* by one because the acid *loses* H^+.)

PROBLEM 1 Draw the conjugate base of each of the following acids:
a. CH_3OH b. $CH_3\overset{+}{N}H_3$ c. CH_3NH_2 d. H_3O^+ e. H_2O

A Base and Its Conjugate Acid

A base is a species that can gain a proton (the Brønsted–Lowry definition). When a base gains a proton (H^+), it forms its conjugate acid. In order to gain a proton, a base must have a lone pair that it can use to form a new bond with the proton.

$CH_3\ddot{O}{:}^-$ (base) + H^+ → $CH_3\ddot{O}{-}H$ (conjugate acid)

Often, the lone pairs and bonding electrons are not shown.

CH_3O^- (base) + H^+ → CH_3OH (conjugate acid)

CH_3NH_2 (base) + H^+ → $CH_3\overset{+}{N}H_3$ (conjugate acid)

CH_3COO^- (base) + H^+ → CH_3COOH (conjugate acid)

Notice that a negatively charged base forms a neutral conjugate acid, whereas a neutral base forms a positively charged conjugate acid. (In each case, the charge *increases* by one because the compound *gains* H^+.)

PROBLEM 2 Draw the conjugate acid of each of the following bases:
a. H_2O b. HO^- c. CH_3OH d. NH_3 e. Cl^-

Acid–Base Reactions

An acid cannot lose a proton unless a base is present to accept the proton. Therefore, an acid always reacts with a base. The reaction of an acid with a base is called an acid–base reaction or a proton transfer reaction. Acid–base reactions are reversible reactions.

CH_3COOH (acid / conjugate acid) + H_2O (base / conjugate base) ⇌ CH_3COO^- (conjugate base / base) + H_3O^+ (conjugate acid / acid)

Notice that an acid reacts with a base in the forward direction (blue labels) and an acid reacts with a base in the reverse direction (red labels).

The Products of an Acid–Base Reaction

Both CH_3COOH and H_2O in the preceding reaction have protons that can be lost (that is, both can act as acids), and both have lone pairs that can form a bond with a proton (that is, both can act as bases). How do we know which reactant will lose a proton and which will gain a proton? We can determine this by comparing the pK_a values of the two reactants; these values are 4.8 for CH_3COOH and 15.7 for H_2O. The stronger acid (the one with the lower pK_a value) will be the one that acts as an acid (it will lose a proton). The other reactant will act as a base (it will gain a proton).

CH_3COOH ($pK_a = 4.8$) + H_2O ($pK_a = 15.7$) ⇌ CH_3COO^- + H_3O^+

PROBLEM 3 Draw the products of the following acid–base reactions:
a. $CH_3\overset{+}{N}H_3$ + H_2O c. $CH_3\overset{+}{N}H_3$ + HO^-
b. HBr + CH_3OH d. CH_3NH_2 + CH_3OH

The Position of Equilibrium

Whether an acid–base reaction favors formation of the products or formation of the reactants can be determined by comparing the pK_a value of the acid that loses a proton in the forward direction with the pK_a value of the acid that loses a proton in the reverse direction. The equilibrium will favor the reaction of the stronger acid to form the weaker acid. The following reaction favors formation of the reactants, because $CH_3\overset{+}{O}H_2$ is a stronger acid than CH_3COOH.

CH_3COOH ($pK_a = 4.8$) + CH_3OH ⇌ CH_3COO^- + $CH_3\overset{+}{O}H_2$ ($pK_a = -1.7$)

Cell Membranes

Cell membranes demonstrate how nonpolar molecules are attracted to other nonpolar molecules, whereas polar molecules are attracted to other polar molecules. All cells are enclosed by a membrane that prevents the aqueous (polar) contents of the cell from pouring out into the aqueous fluid that surrounds the cell. The membrane consists of two layers of phospholipid molecules—called a lipid bilayer. A phospholipid molecule has a polar head and two long nonpolar hydrocarbon tails. The phospholipids are arranged so that the nonpolar tails meet in the center of the membrane. The polar heads are on both the outside surface and the inside surface, where they face the polar solutions on the outside and inside of the cell. Nonpolar cholesterol molecules are found between the tails in order to keep the nonpolar tails from moving around too much. The structure of cholesterol is shown and discussed in Section 3.14.

aqueous exterior of the cell
50 Å
polar head
polar head
cholesterol molecule
aqueous interior of the cell
nonpolar hydrocarbon tails
a phospholipid molecule
the polar head of a phospholipid molecule

a lipid bilayer

New Applications Boxes Throughout!

Numerous new interest boxes throughout each chapter connect chemistry to students' lives and often provide any needed additional explanation on the organic chemistry occurring. New applications include: *Using Genetic Engineering to Treat Ebola, Diseases Caused by a Misfolded Protein, The Inability to Perform an S_N2 Reaction Causes a Severe Clinical Disorder,* and *Electron Delocalization Affects the Three-Dimensional Shape of Proteins.*

Student Tutorials

MasteringChemistry® provides instant feedback specific to the structure or mechanism each student has drawn. Rather than simply providing feedback of the "right/wrong/try again" variety, Mastering recognizes the individual student error by applying evaluators to each problem that analyze chemical accuracy, employing data gathered from all student entries in Mastering, and providing wrong answer-specific feedback that helps students overcome misconceptions. An updated, mobile compatible drawing tool (java-free), provides wrong-answer feedback and guidance on every mechanism problem.

MasteringChemistry® from Pearson is the leading online teaching and learning system designed to improve results by engaging students before, during, and after class with powerful content. Ensure that students arrive ready to learn by assigning educationally effective content before class, and encourage critical thinking and retention with in-class resources such as Learning Catalytics. Students can further master concepts after class through traditional homework assignments that provide hints and answer-specific feedback. The Mastering gradebook records scores for all automatically graded assignments while diagnostic tools give instructors access to rich data to assess student understanding and misconceptions.

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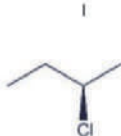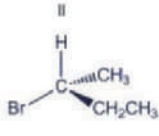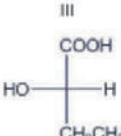
During Class

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Learning Catalytics is a "bring your own device" student engagement, assessment, and classroom intelligence system. With Learning Catalytics you can:

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- Understand immediately where students are and adjust your lecture accordingly.
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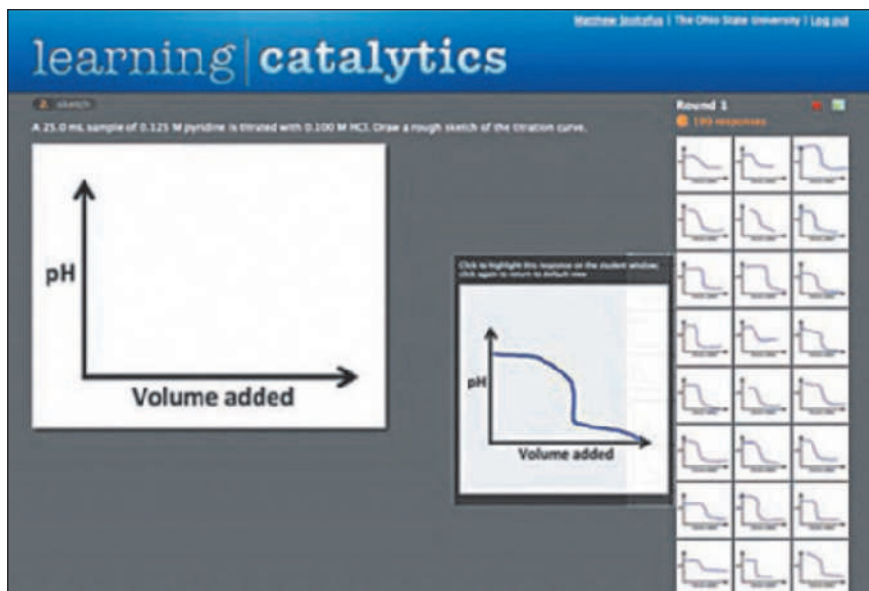

Students learn chemistry by practicing chemistry.

Tutorials, featuring wrong answer-specific feedback, hints, and a wide variety of educationally effective content, guide your students through the toughest topics in chemistry. The hallmark Hints and Feedback offer instruction similar to what students would experience in an office hour, allowing them to learn from their mistakes without being given the answer.

Digital and Print Resources

Essential Organic Chemistry provides an integrated teaching and learning package of support material for both students and professors.

Name of Supplement	Available Online	Instructor or Student Resource	Description
MasteringChemistry® www.masteringchemistry.com	✔	Students & Instructors	MasteringChemistry® from Pearson is the leading online teaching and learning system designed to improve results by engaging students before, during, and after class with powerful content.
Pearson eText ISBN: 0133866890 within MasteringChemistry®	✔	Student	*Essential Organic Chemistry* features a Pearson eText within MasteringChemistry®. The Pearson eText offers students the power to create notes, highlight text in different colors, create bookmarks, zoom, and view single or multiple pages.
TestGen Test Bank	✔	Instructor	Prepared by Ethan Tsai, this resource includes more than 1200 questions in multiple-choice, matching, true/false, and short answer format. Available for download on the Pearson catalog page for *Essential Organic Chemistry* at www.pearsonglobaleditions.com
Instructor Resource Materials	✔	Instructor	Includes all the art, photos, and tables from the book in JPEG format for use in classroom projection or when creating study materials and tests. Available for download on the Pearson catalog page for *Essential Organic Chemistry* at www.pearsonglobaleditions.com

1 Remembering General Chemistry: Electronic Structure and Bonding

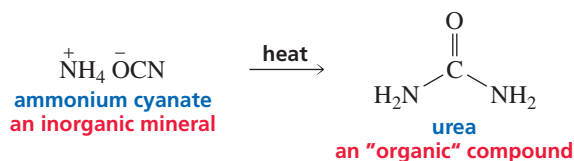
To stay alive, early humans must have been able to distinguish between the different kinds of materials in their world. "You can live on roots and berries," they might have said, "but you can't eat dirt. You can stay warm by burning tree branches, but you can't burn rocks."

By the early eighteenth century, scientists thought they had grasped the nature of that difference, and in 1807 Jöns Jakob Berzelius gave names to the two kinds of materials. Compounds derived from living organisms were believed to contain an immeasurable vital force—the essence of life. These he called "organic." Compounds derived from minerals—those lacking the vital force—were "inorganic."

Because chemists could not create life in the laboratory, they assumed they could not create compounds that had a vital force. Since this was their mind-set, you can imagine how surprised chemists were in 1828 when Friedrich Wöhler produced urea—a compound known to be excreted by mammals—by heating ammonium cyanate, an inorganic mineral.

$$\overset{+}{N}H_4\ \overset{-}{O}CN \xrightarrow{\text{heat}} H_2N{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2$$

ammonium cyanate
an inorganic mineral

urea
an "organic" compound

For the first time, an "organic" compound had been obtained from something other than a living organism and certainly without the aid of any kind of vital force. Chemists, therefore, needed a new definition for "organic compounds." **Organic compounds** are now defined as *compounds that contain carbon*.

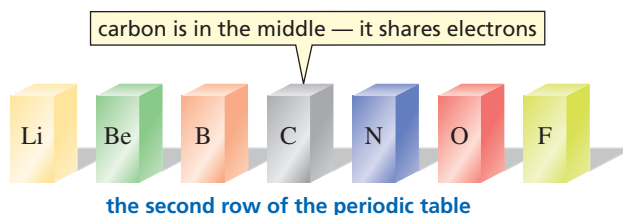
Organic compounds are compounds that contain carbon.

Why is an entire branch of chemistry devoted to the study of carbon-containing compounds? We study organic chemistry because just about all of the molecules that make life possible and that make us who we are—proteins, enzymes, vitamins, lipids, carbohydrates, DNA, RNA—are organic compounds. Thus, the chemical reactions that take

place in living systems, including our own bodies, are reactions of organic compounds. Most of the compounds found in nature—those that we rely on for all of our food, for some of our clothing (cotton, wool, silk), and for energy (natural gas, petroleum)—are organic as well.

Organic compounds are not limited, however, to those found in nature. Chemists have learned how to synthesize millions of organic compounds never found in nature, including synthetic fabrics, plastics, synthetic rubber, and even things like compact discs and Super Glue. And most importantly, almost all of our commonly prescribed drugs are synthetic organic compounds.

Some synthetic organic compounds prevent shortages of naturally occurring products. For example, it has been estimated that if synthetic materials—nylon, polyester, Lycra—were not available for clothing, then all of the arable land in the United States would have to be used for the production of cotton and wool just to provide enough material to clothe us. Other synthetic organic compounds provide us with materials we would not have—Teflon, Plexiglas, Kevlar—if we had only naturally occurring organic compounds. Currently, there are about 16 million known organic compounds, and many more are possible that we cannot even imagine today.

What makes carbon so special? Why are there so many carbon-containing compounds? The answer lies in carbon's position in the periodic table. Carbon is in the center of the second row of elements. We will see that the atoms to the left of carbon have a tendency to give up electrons, whereas the atoms to the right have a tendency to accept electrons (Section 1.3).

Because carbon is in the middle, it neither readily gives up nor readily accepts electrons. Instead, it shares electrons. Carbon can share electrons with several different kinds of atoms, and it can share electrons with other carbon atoms. Consequently, carbon is able to form millions of stable compounds with a wide range of chemical properties simply by sharing electrons.

Natural Organic Compounds Versus Synthetic Organic Compounds

It is a popular belief that natural substances—those made in nature—are superior to synthetic ones—those made in the laboratory. Yet when a chemist synthesizes a compound, such as penicillin or morphine, the compound is exactly the same in all respects as the compound synthesized in nature. Sometimes chemists can even improve on nature. For example, chemists have synthesized analogues of penicillin that do not produce the allergic responses that a significant fraction of the population experiences from naturally produced penicillin, or that do not have the bacterial resistance of the naturally produced antibiotic (Section 16.15). Chemists have also synthesized analogues of morphine—compounds with structures similar to but not identical to that of morphine—that have the same pain-killing effects but, unlike morphine, are not habit forming.

A field of poppies growing in Afghanistan. Most commercial morphine is obtained from opium, the juice extracted from this species of poppy. Morphine is the starting material for the synthesis of heroin. One of the side products formed in the synthesis has an extremely pungent odor; dogs used by drug enforcement agencies are trained to recognize this odor (Section 11.18). Nearly three-quarters of the world's supply of heroin comes from the poppy fields of Afghanistan.

When we study organic chemistry, we learn how organic compounds react. Organic compounds consist of atoms held together by bonds. When an organic compound reacts, some of these bonds break and some new bonds form. *Bonds form when two atoms share electrons, and bonds break when two atoms no longer share electrons*.

How readily a bond forms and how easily it breaks depend on the particular electrons that are shared, which depend, in turn, on the atoms to which the electrons belong. So, if we are going to start our study of organic chemistry at the beginning, we must start with an understanding of the structure of an atom—what electrons an atom has and where they are located.

1.1 THE STRUCTURE OF AN ATOM

An atom consists of a tiny, dense nucleus surrounded by electrons that are spread throughout a relatively large volume of space around the nucleus called an electron cloud. The nucleus contains **positively charged protons** and **uncharged neutrons,** so it is positively charged. The **electrons** are **negatively charged.** The amount of positive charge on a proton equals the amount of negative charge on an electron. Therefore, the number of protons and the number of electrons in an uncharged atom must be the same.

The nucleus contains positively charged protons and uncharged neutrons.

The electrons are negatively charged.

Electrons move continuously. Like anything that moves, electrons have kinetic energy, and this energy is what counteracts the attractive force of the positively charged protons that would otherwise pull the negatively charged electrons into the nucleus.

an atom

Protons and neutrons have approximately the same mass and are about 1800 times more massive than an electron. Most of the *mass* of an atom, therefore, is in its nucleus. Most of the *volume* of an atom, however, is occupied by its electrons, and this is where our focus will be because it is the electrons that form chemical bonds.

The **atomic number** of an atom is the number of protons in its nucleus. The atomic number is unique to a particular element. For example, the atomic number of carbon is 6, which means that all uncharged carbon atoms have six protons and six electrons. Atoms can gain electrons and thereby become negatively charged, or they can lose electrons and become positively charged, but the number of protons in an atom of a particular element never changes.

Although *all carbon atoms have the same atomic number,* they do not all have the same mass number because they do not all have the same number of neutrons. The **mass number** of an atom is the sum of its protons and neutrons. For example, 98.89% of all carbon atoms have six neutrons—giving them a mass number of 12—and 1.11% have seven neutrons—giving them a mass number of 13. These two different kinds of carbon atoms (^{12}C and ^{13}C) are called **isotopes**.

atomic number = the number of protons in the nucleus

mass number = the number of protons + the number of neutrons

isotopes of carbon

Carbon also contains a trace amount of ^{14}C, which has six protons and eight neutrons. This isotope of carbon is radioactive, decaying with a half-life of 5730 years. (The *half-life* is the time it takes for one-half of the nuclei to decay.) As long as a plant or animal is alive, it takes in as much ^{14}C as it excretes or exhales. When it dies, however, it no longer takes in ^{14}C, so the ^{14}C in the organism slowly decreases. Therefore, the age of a substance derived from a living organism can be determined by its ^{14}C content.

The **atomic weight** of an element is the average mass of its atoms. For example, carbon has an atomic number of 12.011 atomic mass units. The **molecular weight** is the *sum of the atomic weights* of all the atoms in a molecule.

atomic weight = the average mass of the atoms in the element

molecular weight = the sum of the atomic weights of all the atoms in the molecule

The bronze sculpture of Albert Einstein, on the grounds of the National Academy of Sciences in Washington, D.C., measures 21 feet from the top of the head to the tip of the feet and weighs 7000 pounds. In his left hand, Einstein holds the mathematical equations that represent his three most important contributions to science: the photoelectric effect, the equivalency of energy and matter, and the theory of relativity. At his feet is a map of the sky.

PROBLEM 1♦

Oxygen has three isotopes, ^{16}O, ^{17}O, and ^{18}O. The atomic number of oxygen is 8. How many protons and neutrons does each of the isotopes have?

1.2 HOW THE ELECTRONS IN AN ATOM ARE DISTRIBUTED

The electrons in an atom can be thought of as occupying a set of concentric shells that surround the nucleus. The first shell is the one closest to the nucleus. The second shell lies farther from the nucleus. The third and higher numbered shells lie even farther out.

Each shell contains subshells known as **atomic orbitals.** The first shell has only an *s* atomic orbital; the second shell has *s* and *p* atomic orbitals; the third shell has *s*, *p*, and *d* atomic orbitals; and the fourth and higher shells consist of *s, p, d*, and *f* atomic orbitals (Table 1.1).

Table 1.1 Distribution of Electrons in the First Four Shells That Surround the Nucleus

	First shell	Second shell	Third shell	Fourth shell
Atomic orbitals	*s*	*s, p*	*s, p, d*	*s, p, d, f*
Number of atomic orbitals	1	1, 3	1, 3, 5	1, 3, 5, 7
Maximum number of electrons	2	8	18	32

Each shell contains one *s* orbital. Each second and higher shell—in addition to its *s* orbital—contains three *p* orbitals. The three *p* orbitals have the same energy. The third and higher shells—in addition to their *s* and *p* orbitals—contain five *d* orbitals, and the fourth and higher shells also contain seven *f* orbitals.

Because a maximum of two electrons can coexist in an atomic orbital (see page 33), the first shell, with only one atomic orbital, can contain no more than two electrons (Table 1.1). The second shell, with four atomic orbitals—one *s* and three *p*—can have a total of eight electrons. Eighteen electrons can occupy the nine atomic orbitals—one *s*, three *p*, and five *d*—of the third shell, and 32 electrons can occupy the 16 atomic orbitals of the fourth shell. In studying organic chemistry, we will be concerned primarily with atoms that have electrons only in the first and second shells.

The **electronic configuration** of an atom describes what orbitals the electrons occupy.

The electronic configurations of the smallest atoms are shown in Table 1.2. (Each arrow—whether pointing up or down—represents one electron.)

Table 1.2 The Electronic Configurations of the Smallest Atoms

Atom	Name of element	Atomic number	1*s*	2*s*	$2p_x$	$2p_y$	$2p_z$	3*s*
H	Hydrogen	1	↑					
He	Helium	2	↑↓					
Li	Lithium	3	↑↓	↑				
Be	Beryllium	4	↑↓	↑↓				
B	Boron	5	↑↓	↑↓	↑			
C	Carbon	6	↑↓	↑↓	↑	↑		
N	Nitrogen	7	↑↓	↑↓	↑	↑	↑	
O	Oxygen	8	↑↓	↑↓	↑↓	↑	↑	
F	Fluorine	9	↑↓	↑↓	↑↓	↑↓	↑	
Ne	Neon	10	↑↓	↑↓	↑↓	↑↓	↑↓	
Na	Sodium	11	↑↓	↑↓	↑↓	↑↓	↑↓	↑

The following three rules specify which orbitals an atom's electrons occupy:

1. **An electron always goes into the available orbital with the lowest energy.**

It is important to remember that the closer the atomic orbital is to the nucleus, the lower is its energy. Because a 1*s* orbital is closer to the nucleus, it is lower in energy than a 2*s* orbital, which is lower in energy—and closer to the nucleus—than a 3*s* orbital. When comparing atomic orbitals in the same shell, we see that an *s* orbital is lower in energy than a *p* orbital, and a *p* orbital is lower in energy than a *d* orbital.

Relative energies of atomic orbitals:

lowest energy → $1s < 2s < 2p < 3s < 3p < 3d$ ← highest energy

2. **No more than two electrons can occupy each atomic orbital, and the two electrons must be of opposite spin.** (Notice in Table 1.2 that spin in one direction is designated by ↑, and spin in the opposite direction is designated by ↓.)

From these first two rules, we can assign electrons to atomic orbitals for atoms that contain one, two, three, four, or five electrons. The single electron of a hydrogen atom occupies a 1*s* orbital, the second electron of a helium atom fills the 1*s* orbital, the third electron of a lithium atom occupies a 2*s* orbital, the fourth electron of a beryllium atom fills the 2*s* orbital, and the fifth electron of a boron atom occupies one of the 2*p* orbitals. (The subscripts *x*, *y*, and *z* distinguish the three 2*p* orbitals.) Because the three *p* orbitals have the same energy, the electron can be put into any one of them. Before we can discuss atoms containing six or more electrons, we need the third rule.

3. **When there are two or more atomic orbitals with the same energy, an electron will occupy an empty orbital before it will pair up with another electron.** In this way, electron repulsion is minimized.

The sixth electron of a carbon atom, therefore, goes into an empty 2*p* orbital, rather than pairing up with the electron already occupying a 2*p* orbital (see Table 1.2). There is one more empty 2*p* orbital, so that is where nitrogen's seventh electron goes. The eighth electron of an oxygen atom pairs up with an electron occupying a 2*p* orbital rather than going into the higher-energy 3*s* orbital.

The locations of the electrons in the remaining elements can be assigned using these three rules.

The electrons in inner shells (those below the outermost shell) are called **core electrons**. The electrons in the outermost shell are called **valence electrons.**

Core electrons are electrons in inner shells.

Valence electrons are electrons in the outermost shell.

Carbon has two core electrons and four valence electrons (Table 1.2). Lithium and sodium each have one valence electron. If you examine the periodic table inside the back cover of this book, you will see that lithium and sodium are in the same column. Elements in the same column of the periodic table have the same number of valence electrons. Because the number of valence electrons is the major factor determining an element's chemical properties, elements in the same column of the periodic table have similar chemical properties. Thus, the chemical behavior of an element depends on its electronic configuration.

The chemical behavior of an element depends on its electronic configuration.

PROBLEM 2♦

How many valence electrons do the following atoms have?

a. boron **b.** nitrogen **c.** oxygen **d.** fluorine

PROBLEM 3♦

How many valence electrons do chlorine, bromine, and iodine have?

PROBLEM 4♦

Look at the relative positions of each pair of atoms listed here in the periodic table. How many core electrons does each have? How many valence electrons does each have?

a. carbon and silicon **b.** oxygen and sulfur **c.** nitrogen and phosphorus

1.3 IONIC AND COVALENT BONDS

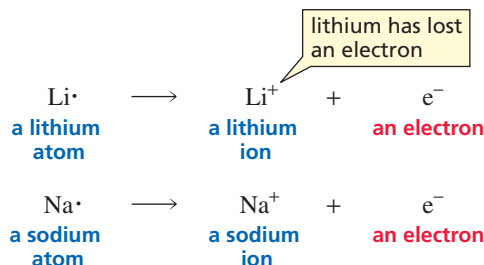
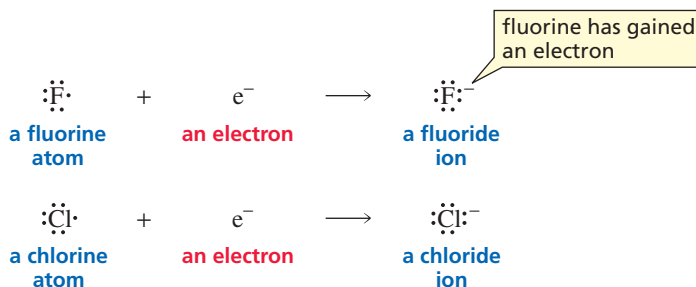
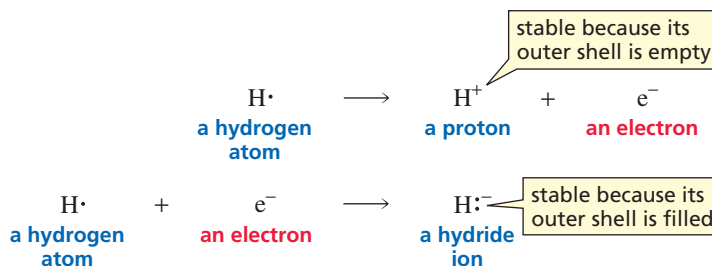
Now that you know about the electronic configuration of atoms, let's look at why atoms come together to form bonds. In explaining why atoms form bonds, G. N. Lewis proposed that

> *An atom is most stable if its outer shell is either filled or contains eight electrons, and it has no electrons of higher energy.*

According to Lewis's theory, an atom will give up, accept, or share electrons in order to achieve a filled outer shell or an outer shell that contains eight electrons. This theory has come to be called the **octet rule** (even though hydrogen needs only two electrons to achieve a filled outer shell).

Lithium (Li) has a single electron in its 2*s* orbital. If it loses this electron, the lithium atom ends up with a filled outer shell—a stable configuration. Lithium, therefore, loses an electron relatively easily. Sodium (Na) has a single electron in its 3*s* orbital, so it too loses an electron easily.

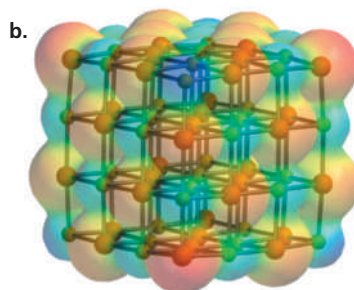
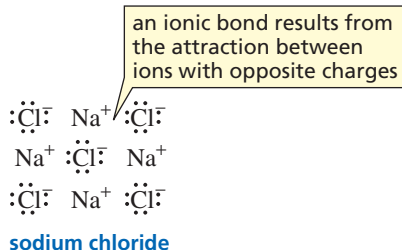
Each of the elements in the first column of the periodic table readily loses an electron because each has a single electron in its outermost shell.

When we draw the electrons around an atom, as in the following equations, core electrons are not shown. Only valence electrons are shown because core electrons are not used in bonding; only valence electrons are used in bonding. Each valence electron is shown as a dot. When the single valence electron of lithium or sodium is removed, the species that is formed is called an ion because it carries a charge.

Fluorine and chlorine each have seven valence electrons. Consequently, each readily acquires an electron in order to have an outer shell of eight electrons, thereby forming F^-, a fluoride ion, and Cl^-, a chloride ion.

A hydrogen atom has one valence electron. Therefore, it can achieve a completely empty shell by losing an electron or a filled outer shell by gaining an electron.

Loss of its sole electron results in a positively charged **hydrogen ion.** A positively charged hydrogen ion is called a **proton** because when a hydrogen atom loses its valence electron, only the hydrogen nucleus—which consists of a single proton—remains. When a hydrogen atom gains an electron, a negatively charged hydrogen ion—called a **hydride ion**—is formed.

PROBLEM 5♦

a. Find potassium (K) in the periodic table and predict how many valence electrons it has.
b. What orbital does the unpaired electron occupy?

Ionic Bonds Are Formed by the Attraction Between Ions of Opposite Charge

We have just seen that sodium gives up an electron easily and chlorine readily acquires an electron, both in order to achieve a filled outer shell. Therefore, when sodium metal and chlorine gas are mixed, each sodium atom transfers an electron to a chlorine atom, and crystalline sodium chloride (table salt) is formed as a result. The positively charged sodium ions and negatively charged chloride ions are held together by the attraction of opposite charges (Figure 1.1).

an ionic bond results from the attraction between ions with opposite charges

$:\ddot{\underset{\cdot\cdot}{Cl}}:^-$ Na^+ $:\ddot{\underset{\cdot\cdot}{Cl}}:^-$
Na^+ $:\ddot{\underset{\cdot\cdot}{Cl}}:^-$ Na^+
$:\ddot{\underset{\cdot\cdot}{Cl}}:^-$ Na^+ $:\ddot{\underset{\cdot\cdot}{Cl}}:^-$

sodium chloride

An ionic bond results from the attraction between ions of opposite charge.

a.
b.
▲ **Figure 1.1**
(a) Crystalline sodium chloride.
(b) The electron-rich chloride ions are red, and the electron-poor sodium ions are blue. Each chloride ion is surrounded by six sodium ions, and each sodium ion is surrounded by six chloride ions. Ignore the sticks holding the balls together; they are there only to keep the model from falling apart.

A **bond** is an attractive force between two ions or between two atoms. A bond that results from the attraction between ions of opposite charge is called an **ionic bond.**

Sodium chloride is an example of an ionic compound. **Ionic compounds** are formed when an element on the left side of the periodic table *transfers* one or more electrons to an element on the right side of the periodic table.

Salar de Uyuni in Bolivia—the largest deposit of natural lithium in the world. Lithium salts are used clinically. Lithium chloride (Li^+Cl^-) is an anti-depressant, lithium bromide (Li^+Br^-) is a sedative, and lithium carbonate ($Li_2^+CO_3^{2-}$) is used to stabilize mood swings in people who suffer from bipolar disorder. Scientists do not yet know why lithium salts have these therapeutic effects.

Covalent Bonds Are Formed by Sharing a Pair of Electrons

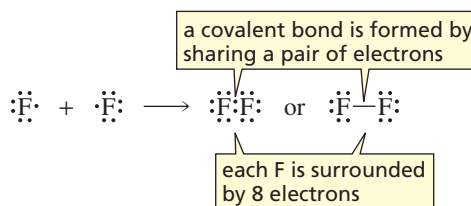
Instead of giving up or acquiring electrons to achieve a filled outer shell, an atom can achieve a filled outer shell by sharing a pair of electrons. For example, two fluorine atoms can each attain a filled second shell by sharing their unpaired valence electrons.

A bond formed as a result of sharing electrons is called a **covalent bond.** A covalent bond is commonly shown by a solid line rather than as a pair of dots.

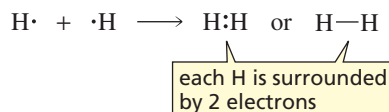
A covalent bond is formed when two atoms share a pair of electrons.

$$:\ddot{\underset{..}{F}}\cdot + \cdot\ddot{\underset{..}{F}}: \longrightarrow :\ddot{\underset{..}{F}}:\ddot{\underset{..}{F}}: \text{ or } :\ddot{\underset{..}{F}}-\ddot{\underset{..}{F}}:$$

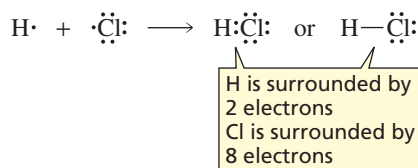
a covalent bond is formed by sharing a pair of electrons

each F is surrounded by 8 electrons

Two hydrogen atoms can form a covalent bond by sharing electrons. As a result of covalent bonding, each hydrogen acquires a stable, filled first shell.

$$H\cdot + \cdot H \longrightarrow H:H \text{ or } H-H$$

each H is surrounded by 2 electrons

Similarly, hydrogen and chlorine can form a covalent bond by sharing electrons. In doing so, hydrogen fills its only shell, and chlorine achieves an outer shell of eight electrons.

$$H\cdot + \cdot\ddot{\underset{..}{Cl}}: \longrightarrow H:\ddot{\underset{..}{Cl}}: \text{ or } H-\ddot{\underset{..}{Cl}}:$$

H is surrounded by 2 electrons
Cl is surrounded by 8 electrons

We just saw that because hydrogen has one valence electron and chlorine has seven valence electrons, each can achieve a filled outer shell by forming one covalent bond. Oxygen, however, has six valence electrons, so it needs to form two covalent bonds to achieve an outer shell of eight electrons. Nitrogen, with five valence electrons, must form three covalent bonds, and carbon, with four valence electrons, must form four covalent bonds to achieve a filled outer shell. Notice that all the atoms in water, ammonia, and methane have filled outer shells.

$$2\,H\cdot + \cdot\ddot{\underset{.}{O}}: \longrightarrow H-\ddot{\underset{|\atop H}{O}}:$$

oxygen forms 2 covalent bonds

water

$$3\,H\cdot + \cdot\ddot{\underset{.}{N}}\cdot \longrightarrow H-\ddot{\underset{|\atop H}{N}}-H$$

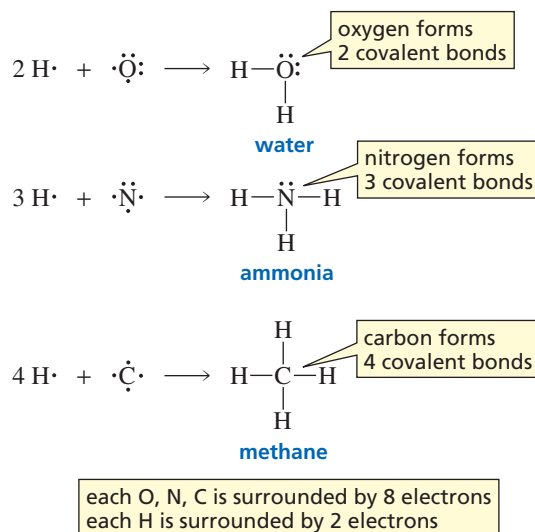
nitrogen forms 3 covalent bonds

ammonia

$$4\,H\cdot + \cdot\dot{\underset{.}{C}}\cdot \longrightarrow H-\overset{H\atop |}{\underset{|\atop H}{C}}-H$$

carbon forms 4 covalent bonds

methane

each O, N, C is surrounded by 8 electrons
each H is surrounded by 2 electrons

Nonpolar Covalent Bonds and Polar Covalent Bonds

A nonpolar covalent bond is a covalent bond between atoms with the same electronegativity.

The atoms that share the bonding electrons in the F—F and H—H covalent bonds are identical. Therefore, they share the electrons equally; that is, each electron spends as much time in the vicinity of one atom as in that of the other. Such a bond is called a **nonpolar covalent bond.**

In contrast, the bonding electrons in hydrogen chloride, water, and ammonia are more attracted to one atom than to another because the atoms that share the electrons in these molecules are different and have different electronegativities.

Electronegativity is a measure of the ability of an atom to pull the bonding electrons toward itself. The bonding electrons in hydrogen chloride, water, and ammonia are more attracted to the atom with the greater electronegativity. The bonds in these compounds are **polar covalent bonds.**

A polar covalent bond is a covalent bond between atoms with different electronegativities.

The electronegativities of some of the elements are shown in Table 1.3. Notice that electronegativity increases from left to right across a row of the periodic table and from bottom to top in any of the columns.

Table 1.3 The Electronegativities of Selected Elements[a]

1A	2A		3A	4A	5A	6A	7A
H 2.1							
Li 1.0	Be 1.5		B 2.0	C 2.5	N 3.0	O 3.5	F 4.0
Na 0.9	Mg 1.2		Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0
K 0.8	Ca 1.0						Br 2.8
							I 2.5

increasing electronegativity (left to right)

increasing electronegativity (bottom to top)

[a]Electronegativity values are relative, not absolute. As a result, there are several scales of electronegativities. The electronegativities listed here are from the scale devised by Linus Pauling.

A polar covalent bond has a slight positive charge on one end and a slight negative charge on the other. Polarity in a covalent bond is indicated by the symbols δ^+ and δ^-, which denote partial positive and partial negative charges. The negative end of the bond is the end that has the more electronegative atom. The greater the difference in electronegativity between the bonded atoms, the more polar the bond will be.

$\overset{\delta+}{H}—\overset{\delta-}{Cl}$ $\overset{\delta+}{H}—\overset{\delta-}{O}—\overset{\delta+}{H}$ $\overset{\delta+}{H}—\overset{\delta-}{N}(—\overset{\delta+}{H})—\overset{\delta+}{H}$

The direction of bond polarity can be indicated with an arrow. By convention, chemists draw the arrow so that it points in the direction in which the electrons are pulled. Thus, the head of the arrow is at the negative end of the bond; a short perpendicular line near the tail of the arrow marks the positive end of the bond. (Physicists draw the arrow in the opposite direction.)

H—Cl: (the negative end of the bond)

You can think of ionic bonds and nonpolar covalent bonds as being at the opposite ends of a continuum of bond types. All bonds fall somewhere on this line. At one end is an ionic bond—a bond in which no electrons are shared. At the other end is a nonpolar covalent bond—a bond in which the electrons are shared equally. Polar covalent bonds fall somewhere in between.

The greater the difference in electronegativity between the atoms forming the bond, the closer the bond is to the ionic end of the continuum.

C—H bonds are relatively nonpolar, because carbon and hydrogen have similar electronegativities (electronegativity difference = 0.4; see Table 1.3); N—H bonds are more polar (electronegativity difference = 0.9), but not as polar as O—H bonds (electronegativity difference = 1.4). Even closer to the ionic end of the continuum is the bond between sodium and chloride ions (electronegativity difference = 2.1), but sodium chloride is not as ionic as potassium fluoride (electronegativity difference = 3.2).

PROBLEM 6♦

Which bond is more polar?

a. H—CH_3 or :C̤̈l—CH_3 **c.** H—C̤̈l: or H—F̤̈:

b. H—Ö̤H or H—H **d.** :C̤̈l—C̤̈l: or :C̤̈l—CH_3

PROBLEM 7♦

Which of the following has

a. the most polar bond? **b.** the least polar bond?

NaI LiBr Cl_2 KCl

A polar bond has a **dipole**—it has a negative end and a positive end. The size of the dipole is indicated by the dipole moment μ, which is reported in a unit called a **debye (D)** (pronounced de-bye). The **dipole moments** of some bonds commonly found in organic compounds are listed in Table 1.4.

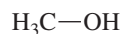
dipole moment of a bond = the size of the charge × the distance between the charges

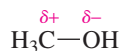
Table 1.4 The Dipole Moments of Some Commonly Encountered Bonds

Bond	Dipole moment (D)	Bond	Dipole moment (D)
H—C	0.4	C—C	0
H—N	1.3	C—N	0.2
H—O	1.5	C—O	0.7
H—F	1.7	C—F	1.6
H—Cl	1.1	C—Cl	1.5
H—Br	0.8	C—Br	1.4
H—I	0.4	C—I	1.2

PROBLEM 8 Solved

Use the symbols δ^+ and δ^- to show the direction of the polarity of the indicated bond:

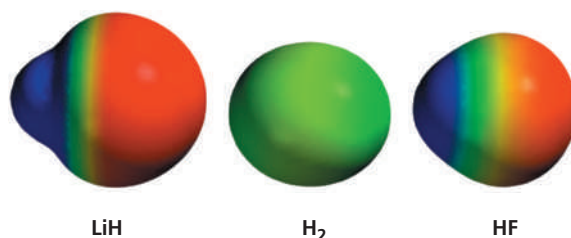
H_3C—OH

Solution The indicated bond is between carbon and oxygen. According to Table 1.3, the electronegativity of carbon is 2.5 and the electronegativity of oxygen is 3.5. Because oxygen is more electronegative than carbon, oxygen has a partial negative charge and carbon has a partial positive charge.

$$\overset{\delta+}{H_3C}-\overset{\delta-}{O}H$$

PROBLEM 9♦

Use the symbols δ^+ and δ^- to show the direction of the polarity of the indicated bond in each of the following compounds:

a. $HO-H$ **c.** H_3C-NH_2 **e.** $HO-Br$ **g.** $I-Cl$

b. $F-Br$ **d.** H_3C-Cl **f.** H_3C-Li **h.** H_2N-OH

Electrostatic potential maps (often called simply potential maps) are models that show how charge is distributed in the molecule under the map. The potential maps for LiH, H_2, and HF are shown here.

The colors on a potential map indicate the relative distribution of charge in the molecule. Red, signifying the most negative electrostatic potential, is used for regions that attract electron-deficient species most strongly. Blue is used for areas with the most positive electrostatic potential—regions that attract electron-rich species most strongly. Other colors indicate intermediate levels of attraction.

The potential map for LiH shows that the hydrogen atom (red) is more electron-rich than the lithium atom (blue). By comparing the three maps, we can tell that the hydrogen in LiH is more electron-rich than a hydrogen in H_2, whereas the hydrogen in HF is less electron-rich than a hydrogen in H_2.

Because a potential map roughly marks the "edge" of the molecule's electron cloud, the map tells us something about the relative size and shape of the molecule. A given kind of atom can have different sizes in different molecules, because the size of an atom in a potential map depends on its electron density. For example, the negatively charged hydrogen in LiH is bigger than a neutral hydrogen in H_2, which is bigger than the positively charged hydrogen in HF.

PROBLEM 10♦

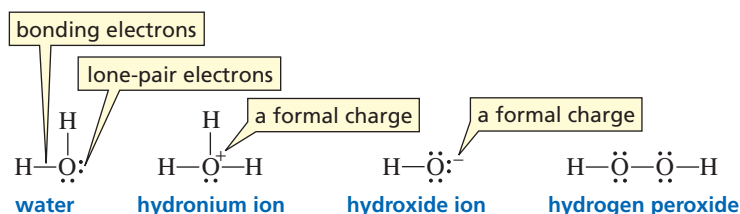
After examining the potential maps for LiH, HF, and H_2, answer the following questions:

a. Which compounds are polar?
b. Why does LiH have the largest hydrogen?

1.4 HOW THE STRUCTURE OF A COMPOUND IS REPRESENTED

First we will see how compounds are drawn using Lewis structures. Then we will look at the kinds of structures that are used more commonly for organic compounds.

Lewis Structures

The chemical symbols we have been using, in which the valence electrons are represented as dots or solid lines, are called **Lewis structures.** Lewis structures show us which atoms are bonded together and tell us whether any atoms possess *lone-pair electrons* or have a *formal charge*, two concepts described below. The Lewis structures for H_2O, H_3O^+, HO^-, and H_2O_2 are shown here.

Notice that the atoms in Lewis structures are always lined up linearly or at right angles. Therefore, they do not tell us anything about the bond angles in the actual molecule.

When you draw a Lewis structure, make sure that hydrogen atoms are surrounded by two electrons and that C, O, N, and halogen (F, Cl, Br, I) atoms are surrounded by eight electrons, in accordance with the octet rule. Valence electrons not used in bonding are called **nonbonding electrons** or **lone-pair electrons.**

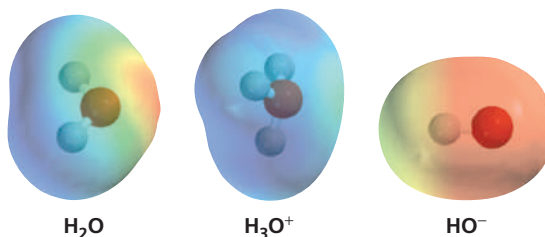
Lone-pair electrons are valence electrons that do not form bonds.

Once you have the atoms and the electrons in place, you must examine each atom to see whether a formal charge should be assigned to it. A **formal charge** is the *difference* between the number of valence electrons an atom has when it is not bonded to any other atoms and the number it "owns" when it is bonded. An atom "owns" all of its lone-pair electrons and half of its bonding (shared) electrons.

formal charge = number of valence electrons
− (number of lone-pair electrons + 1/2 number of bonding electrons)

For example, an oxygen atom has six valence electrons (Table 1.2). In water (H_2O), oxygen "owns" six electrons (four lone-pair electrons and half of the four bonding electrons). Because the number of electrons it "owns" is equal to the number of its valence electrons ($6 - 6 = 0$), the oxygen atom in water does not have a formal charge.

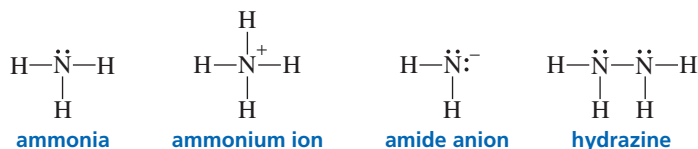
The oxygen atom in the hydronium ion (H_3O^+) "owns" five electrons: two lone-pair electrons plus three (half of six) bonding electrons. Because the number of electrons oxygen "owns" is one less than the number of its valence electrons ($6 - 5 = 1$), its formal charge is $+1$.

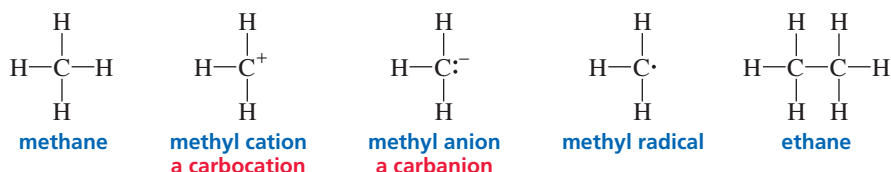
The oxygen atom in the hydroxide ion (HO^-) "owns" seven electrons: six lone-pair electrons plus one (half of two) bonding electron. Because oxygen "owns" one more electron than the number of its valence electrons ($6 - 7 = -1$), its formal charge is -1.

PROBLEM 11♦

An atom with a formal charge does not necessarily have more or less electron density than the atoms in the molecule without formal charges. We can see this by examining the potential maps for H_2O, H_3O^+, and HO^- on page 40.

a. Which atom bears the formal negative charge in the hydroxide ion?
b. Which atom has the greater electron density in the hydroxide ion?
c. Which atom bears the formal positive charge in the hydronium ion?
d. Which atom has the least electron density in the hydronium ion?

Nitrogen has five valence electrons (Table 1.2). Prove to yourself that the appropriate formal charges have been assigned to the nitrogen atoms in the following Lewis structures:

ammonia · ammonium ion · amide anion · hydrazine

Carbon has four valence electrons. Take a moment to make sure you understand why the carbon atoms in the following Lewis structures have the indicated formal charges:

methane · methyl cation (a carbocation) · methyl anion (a carbanion) · methyl radical · ethane

A species containing a positively charged carbon is called a **carbocation,** and a species containing a negatively charged carbon is called a **carbanion.** (Recall that a *cation* is a positively charged ion and an *anion* is a negatively charged ion.) A species containing an atom with a single unpaired electron is called a **radical** (often called a **free radical**).

A carbocation is a species that contains a positively charged carbon.

A carbanion is a species that contains a negatively charged carbon.

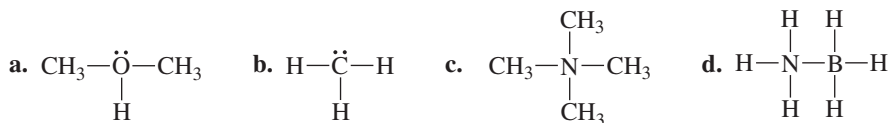
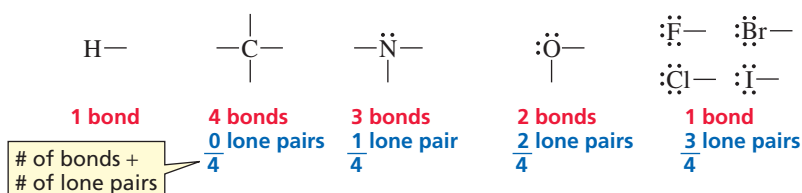
A radical is a species that contains an atom with an unpaired electron.

Hydrogen has one valence electron, and each halogen (F, Cl, Br, I) has seven valence electrons, so the following species have the indicated formal charges:

H^+ hydrogen ion · $H:^-$ hydride ion · $H\cdot$ hydrogen radical · $:\ddot{Br}:^-$ bromide ion · $:\ddot{Br}\cdot$ bromine radical · $:\ddot{Br}-\ddot{Br}:$ bromine · $:\ddot{Cl}-\ddot{Cl}:$ chlorine

PROBLEM 12

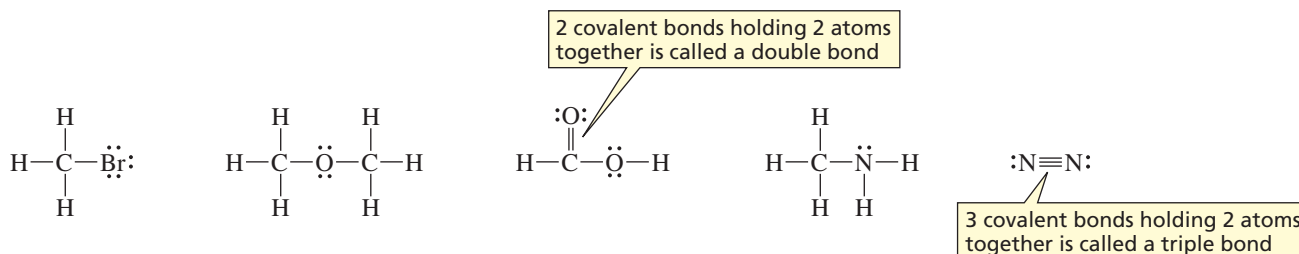
Give each atom the appropriate formal charge:

a. $CH_3-\ddot{O}(H)-CH_3$ **b.** $H-\ddot{C}(H)-H$ **c.** $CH_3-N(CH_3)(CH_3)-CH_3$ **d.** $H-N(H)(H)-B(H)(H)-H$

While studying the molecules in this section, notice that when the atoms do not bear a formal charge or an unpaired electron, hydrogen always has *one* covalent bond, carbon always has *four* covalent bonds, nitrogen always has *three* covalent bonds, oxygen always has *two* covalent bonds, and a halogen always has *one* covalent bond. Also notice that nitrogen has one lone pair, oxygen has two lone pairs, and a halogen has three lone pairs, because in order to have a complete octet, the number of bonds and the number of lone pairs must total four.

When it is neutral:
H forms 1 bond
C forms 4 bonds
N forms 3 bonds
O forms 2 bonds
a halogen forms 1 bond

Atoms that have more bonds or fewer bonds than the number required for a neutral atom will have either a formal charge or an unpaired electron. These numbers are very important to remember when you are first drawing structures of organic compounds because they provide a quick way to recognize when you have made a mistake.

Each atom in the following Lewis structures has a filled outer shell. Notice that since none of the molecules has a formal charge or an unpaired electron, H forms 1 bond, C forms 4 bonds, N forms 3 bonds, O forms 2 bonds, and Br forms 1 bond. Notice, too, that each N has 1 lone pair, each O has 2 lone pairs, and Br has 3 lone pairs.

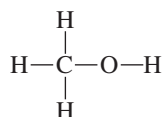
2 covalent bonds holding 2 atoms together is called a double bond

3 covalent bonds holding 2 atoms together is called a triple bond

PROBLEM-SOLVING STRATEGY

Drawing Lewis Structures

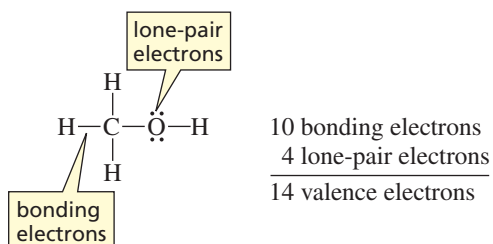
a. Draw the Lewis structure for CH_4O. **b.** Draw the Lewis structure for HNO_2.

a. 1. Determine the total number of valence electrons (4 for C, 1 for each H, and 6 for O adds up to $4 + 4 + 6 = 14$ valence electrons).

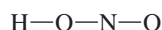
2. Distribute the atoms, remembering that C forms four bonds, O forms two bonds, and each H forms one bond. Always put the hydrogens on the outside of the molecule since H can form only one bond.

3. Use the total number of valence electrons to form bonds and fill octets with lone-pair electrons.

lone-pair electrons

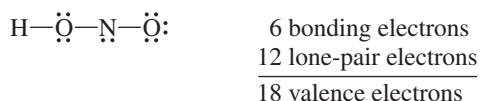
bonding electrons

10 bonding electrons
4 lone-pair electrons
14 valence electrons

4. Assign a formal charge to any atom whose number of valence electrons is not equal to the number of its lone-pair electrons plus one-half of its bonding electrons. (None of the atoms in CH_4O has a formal charge.)

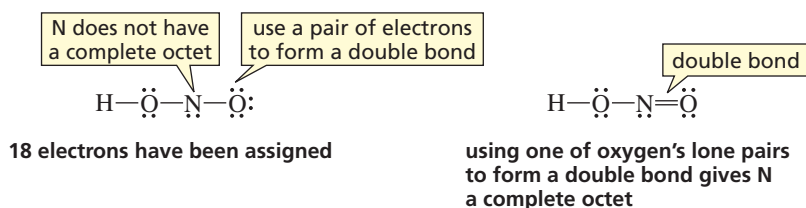
b. 1. Determine the total number of valence electrons (1 for H, 5 for N, and 6 for each O adds up to $1 + 5 + 12 = 18$ valence electrons).

2. Distribute the atoms putting the hydrogen on the outside of the molecule. If a species has two or more oxygen atoms, avoid oxygen–oxygen single bonds. These are weak bonds, and few compounds have them.

H—O—N—O

3. Use the total number of valence electrons to form bonds and fill octets with lone-pair electrons.

6 bonding electrons
12 lone-pair electrons
18 valence electrons

4. If, after all the electrons have been assigned, an atom (other than hydrogen) does not have a complete octet, use a lone pair to form a double bond to that atom.

18 electrons have been assigned

using one of oxygen's lone pairs to form a double bond gives N a complete octet

5. Assign a formal charge to any atom whose number of valence electrons is not equal to the number of its lone-pair electrons plus one-half of its bonding electrons. (None of the atoms in HNO_2 has a formal charge.)

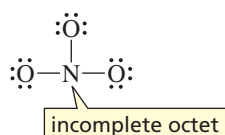
Now use the strategy you have just learned to solve Problem 13.

PROBLEM 13 Solved

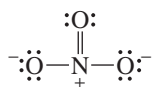
Draw the Lewis structure for each of the following:

a. NO_3^- **b.** NO_2^+ **c.** $^-C_2H_5$ **d.** $^+C_2H_5$ **e.** $CH_3\overset{+}{N}H_3$

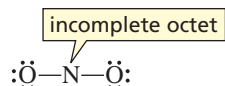
Solution to 13a The total number of valence electrons is 23 (5 for N and 6 for each of the three Os). Because the species has one negative charge, we must add 1 to the number of valence electrons, for a total of 24. The only way we can arrange one N and three Os and avoid O—O single bonds is to place the three Os around the N. We then use the 24 electrons to form bonds and fill octets with lone-pair electrons.

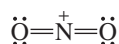
:Ö:
|
:Ö—N—Ö:

incomplete octet

All 24 electrons have been assigned, but N does not have a complete octet. We complete N's octet by using one of oxygen's lone pairs to form a double bond. (It does not make a difference which oxygen atom we choose.) When we check each atom to see whether it has a formal charge, we find that two of the Os are negatively charged and the N is positively charged, for an overall charge of −1.

:O:
‖
⁻:Ö—N—Ö:⁻
+

Solution to 13b The total number of valence electrons is 17 (5 for N and 6 for each of the two Os). Because the species has one positive charge, we must subtract 1 from the number of valence electrons, for a total of 16. The 16 electrons are used to form bonds and fill octets with lone-pair electrons.

incomplete octet

:Ö—N—Ö:

Two double bonds are necessary to complete N's octet. We find that the N has a formal charge of +1.

Ö=$\overset{+}{N}$=Ö

PROBLEM 14♦

a. Draw two Lewis structures for C_2H_6O. **b.** Draw three Lewis structures for C_3H_8O.

(*Hint:* The two Lewis structures in part **a** are **constitutional isomers**—molecules that have the same atoms, but differ in the way the atoms are connected. The three Lewis structures in part **b** are also constitutional isomers.)

Kekulé Structures and Condensed Structures

Kekulé structures are like Lewis structures except lone pairs are normally omitted. Structures are often further simplified by omitting some (or all) of the covalent bonds and listing atoms bonded to a particular carbon (or nitrogen or oxygen) next to it (with a subscript if there is more than one of a particular atom). Lone-pair electrons are usually not shown, unless they are needed to draw attention to some chemical property of the molecule. These structures are called **condensed structures.** Compare the condensed structures shown here with the Lewis structures shown on page 42.

CH_3Br $\quad$ CH_3OCH_3 $\quad$ HCO_2H $\quad$ CH_3NH_2 $\quad$ N_2

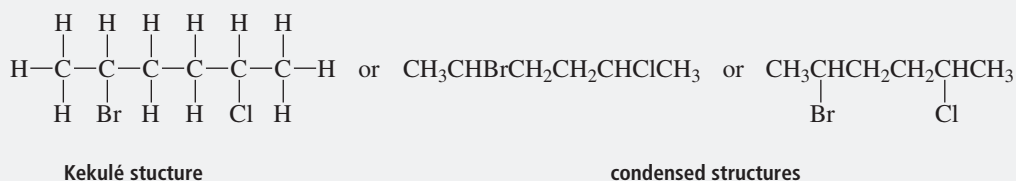
(Although lone pairs are not shown, you should remember that neutral nitrogen, oxygen, and halogen atoms always have them: one pair for nitrogen, two pairs for oxygen, and three pairs for a halogen.)

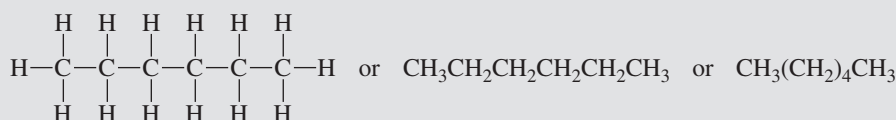
You can find examples of Kekulé and condensed structures as well as the conventions commonly used to create condensed structures in Table 1.5. Notice that since none of the molecules in Table 1.5 has a formal charge or an unpaired electron, each C has four bonds, each N has three bonds, each O has two bonds, and each H or halogen has one bond.

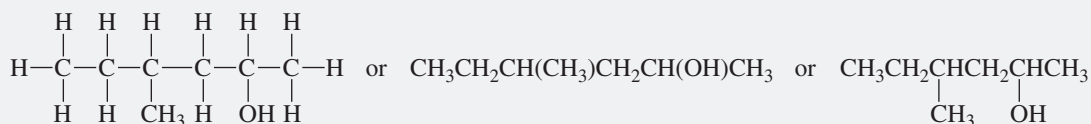
Table 1.5 Kekulé Structures and Condensed Structures

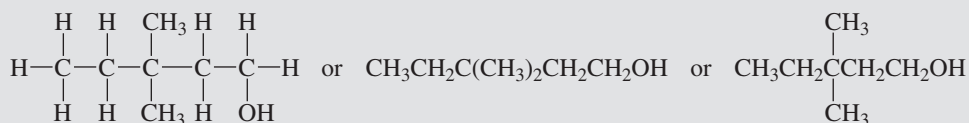
Atoms bonded to a carbon are shown to the right of the carbon. Atoms other than H can be shown hanging from the carbon.

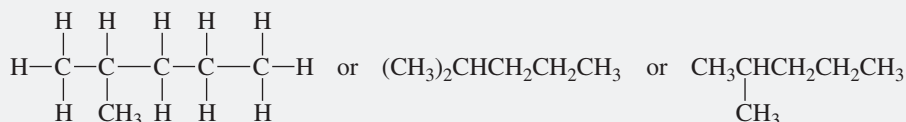
```
   H  H  H  H  H  H
   |  |  |  |  |  |
H—C—C—C—C—C—C—H   or  CH3CHBrCH2CH2CHClCH3   or  CH3CHCH2CH2CHCH3
   |  |  |  |  |  |                                    |        |
   H  Br H  H  Cl H                                    Br       Cl
```

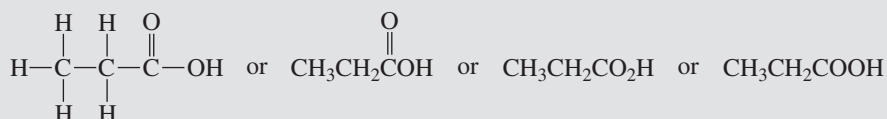
Kekulé stucture $\qquad$ **condensed structures**

Repeating CH_2 groups can be shown in parentheses.

```
   H  H  H  H  H  H
   |  |  |  |  |  |
H—C—C—C—C—C—C—H   or  CH3CH2CH2CH2CH2CH3   or  CH3(CH2)4CH3
   |  |  |  |  |  |
   H  H  H  H  H  H
```

Groups bonded to a carbon can be shown (in parentheses) to the right of the carbon, or hanging from the carbon.

```
   H  H  H    H  H  H
   |  |  |    |  |  |
H—C—C—C——C—C—C—H   or  CH3CH2CH(CH3)CH2CH(OH)CH3   or  CH3CH2CHCH2CHCH3
   |  |  |    |  |  |                                          |     |
   H  H  CH3  H  OH H                                          CH3   OH
```

A single group bonded to the far-right carbon is not put in parentheses.

```
   H  H  CH3 H  H                                       CH3
   |  |  |   |  |                                       |
H—C—C—C——C—C—H   or  CH3CH2C(CH3)2CH2CH2OH   or  CH3CH2CCH2CH2OH
   |  |  |   |  |                                       |
   H  H  CH3 H  OH                                      CH3
```

Two or more identical groups bonded to the "first" atom on the left can be shown (in parentheses) to the left of that atom, or hanging from the atom.

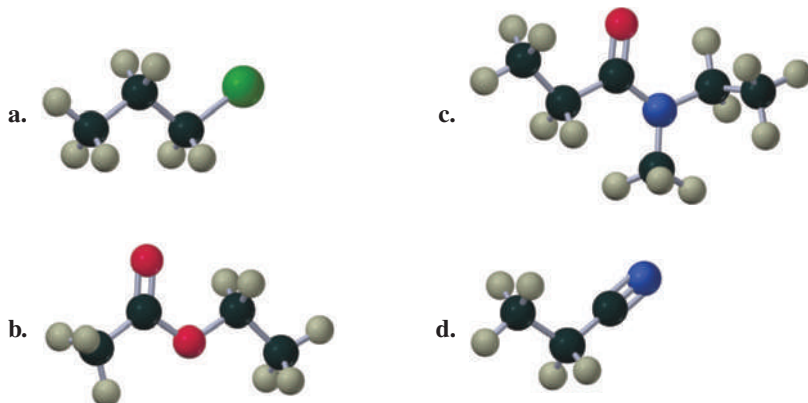
```
   H  H    H  H    H
   |  |    |  |    |
H—C—C——C—C——C—H   or  (CH3)2CHCH2CH2CH3   or  CH3CHCH2CH2CH3
   |  |    |  |    |                              |
   H  CH3  H  H    H                              CH3
```

An oxygen doubly bonded to a carbon can be shown hanging from the carbon or to the right of the carbon.

```
   H  H  O                    O
   |  |  ||                   ||
H—C—C—C—OH   or  CH3CH2COH   or  CH3CH2CO2H   or  CH3CH2COOH
   |  |
   H  H
```

PROBLEM 15♦

Draw the lone-pair electrons that are not shown in the following condensed structures:

a. $CH_3CH_2NH_2$ **c.** CH_3CH_2OH **e.** CH_3CH_2Cl
b. CH_3NHCH_3 **d.** CH_3OCH_3 **f.** $HONH_2$

PROBLEM 16♦

Draw condensed structures for the compounds represented by the following models (black = C, gray = H, red = O, blue = N, and green = Cl):

PROBLEM 17♦

Which of the atoms in the molecular models in Problem 16 have

a. three lone pairs? **b.** two lone pairs? **c.** one lone pair? **d.** no lone pairs?

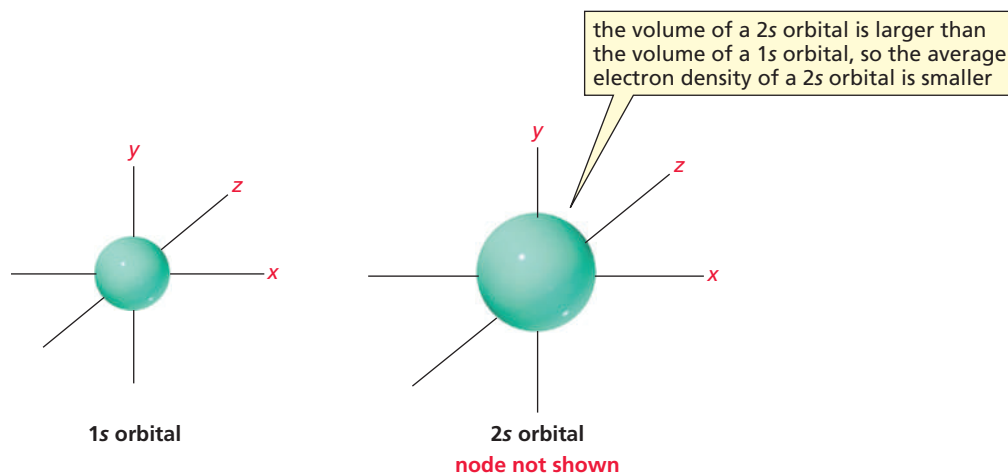
PROBLEM 18

Convert the following condensed structures to Kekulé structures, showing the covalent bonds:

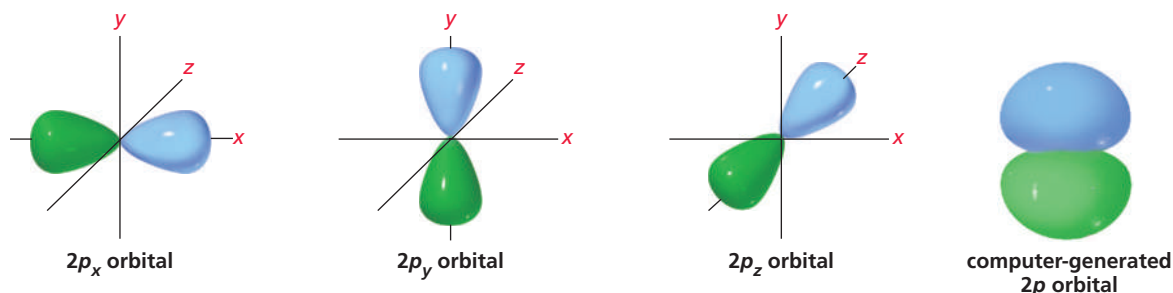
a. $CH_3NH(CH_2)_2CH_3$ **b.** $(CH_3)_2CHCl$ **c.** $(CH_3)_3CBr$ **d.** $(CH_3)_3C(CH_2)_3CHO$

1.5 ATOMIC ORBITALS

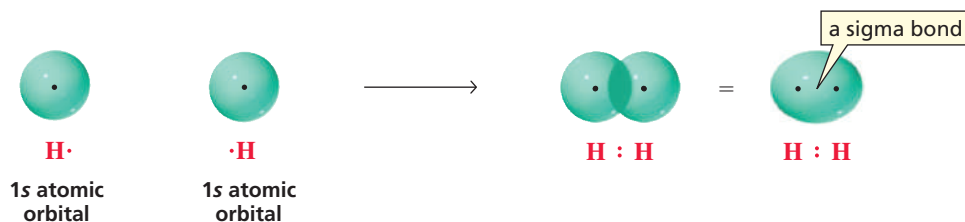
We have seen that electrons are distributed into different atomic orbitals (Table 1.2). An atomic orbital is a three-dimensional region around the nucleus where an electron is most likely to be found.

But what does an orbital look like? An *s* atomic orbital is a sphere with the nucleus at its center. Thus, when we say that an electron occupies a 1*s* orbital, we mean that there is a greater than 90% probability that the electron is in the space defined by the sphere.

An atomic orbital is the three-dimensional region around the nucleus where an electron is most likely to be found.

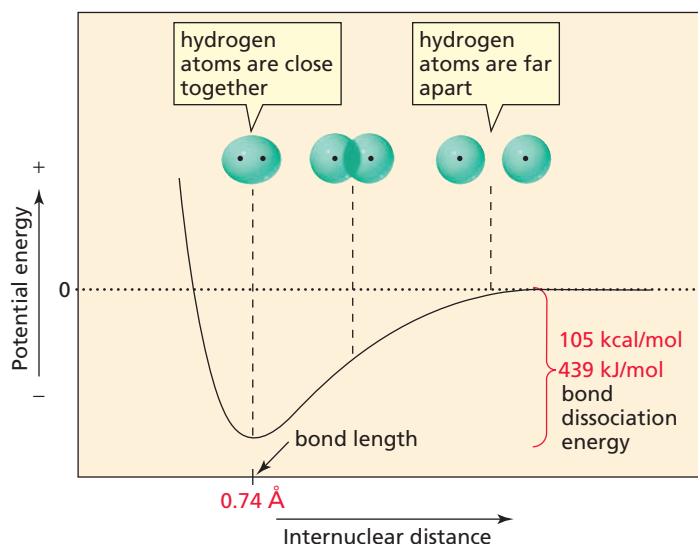
Because the second shell lies farther from the nucleus than the first shell (Section 1.2), the average distance from the nucleus is greater for an electron in a 2*s* orbital than it is for an electron in a 1*s* orbital. A 2*s* orbital, therefore, is represented by a larger sphere. Because of the greater size of a 2*s* orbital, its average electron density is less than the average electron density of a 1*s* orbital.

Unlike *s* orbitals, which resemble spheres, *p* orbitals have two lobes. Generally, the lobes are depicted as teardrop shaped, but computer-generated representations reveal that they are shaped more like doorknobs (as shown on the right below).

In Section 1.2, we saw that the second and higher numbered shells each contain three *p* orbitals, and the three *p* orbitals have the same energy. The p_x orbital is symmetrical about the *x*-axis, the p_y orbital is symmetrical about the *y*-axis, and the p_z orbital is symmetrical about the *z*-axis. This means that each *p* orbital is perpendicular to the other two *p* orbitals. The energy of a 2*p* orbital is slightly greater than that of a 2*s* orbital because the average location of an electron in a 2*p* orbital is farther away from the nucleus.

1.6 HOW ATOMS FORM COVALENT BONDS

How do atoms form covalent bonds in order to form molecules? Let's look first at the bonding in a hydrogen molecule (H_2). The covalent bond is formed when the 1*s* orbital of one hydrogen atom overlaps the 1*s* orbital of a second hydrogen atom. The covalent bond that is formed when the two orbitals overlap is called a **sigma (σ) bond.**

Why do atoms form covalent bonds? As the two orbitals start to overlap to form the covalent bond, energy is released (and stability increases) because the electron in each atom is attracted both to its own nucleus and to the positively charged nucleus of the other atom (Figure 1.2). Thus, atoms form covalent bonds because the covalently bonded atoms are more stable than the individual atoms. The attraction of the negatively charged electrons for the positively charged nuclei is what holds the atoms together. The more the orbitals overlap, the more the energy decreases until the atoms are so close together that their positively charged nuclei start to repel each other. This repulsion causes a large increase in energy. Maximum stability (that is, minimum energy) is achieved when the nuclei are a certain distance apart. This distance is the **bond length** of the new covalent bond. The length of the H—H bond is 0.74 Å (1Å = 10^{-8}cm).

As Figure 1.2 shows, energy is released when a covalent bond forms. When the H—H bond forms, 105 kcal/mol or 439 kJ/mol of energy is released (1 kcal = 4.184 kJ).* Breaking the bond requires precisely the same amount of energy. Thus, the

*Joules are the Système International (SI) units for energy, although many chemists use calories. We will use both in this book.

Maximum stability corresponds to minimum energy.

◀ **Figure 1.2**
The change in energy that occurs as two 1*s* atomic orbitals approach each other. The internuclear distance at minimum energy is the length of the H—H covalent bond.

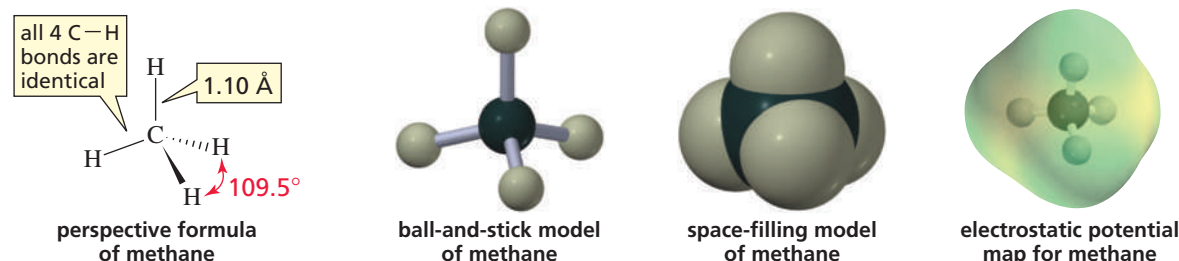
bond strength—also called the **bond dissociation energy**—is the energy required to break the bond, or the energy released when the bond is formed. Every covalent bond has a characteristic bond length and bond strength.

1.7 HOW SINGLE BONDS ARE FORMED IN ORGANIC COMPOUNDS

We will begin the discussion of bonding in organic compounds by looking at the bonding in methane, a compound with only one carbon. Then we will examine the bonding in ethane, a compound with two carbons attached by a carbon–carbon single bond.

The Bonds in Methane

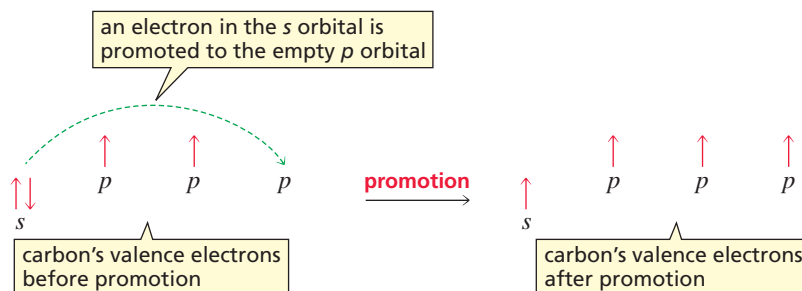
Methane (CH_4) has four covalent C—H bonds. Because all four bonds have the same length (1.10 Å) and all the bond angles are the same (109.5°), we can conclude that the four C—H bonds in methane are identical. Four different ways to represent a methane molecule are shown here.

perspective formula of methane **ball-and-stick model of methane** **space-filling model of methane** **electrostatic potential map for methane**

In a **perspective formula,** bonds in the plane of the paper are drawn as solid lines (and they must be adjacent to one another), a bond protruding out of the plane of the paper toward the viewer is drawn as a solid wedge, and one projecting back from the plane of the paper away from the viewer is drawn as a hatched wedge.

The potential map of methane shows that neither carbon nor hydrogen carries much of a charge: there are neither red areas, representing partially negatively charged atoms, nor blue areas, representing partially positively charged atoms. (Compare this map with the potential map for water on page 57.) The absence of partially charged atoms can be explained by the similar electronegativities of carbon and hydrogen, which cause them to share their bonding electrons relatively equally. Methane, therefore, is a **nonpolar molecule.**

The blue colors of Uranus and Neptune are caused by the presence of methane, an odorless gas, in their atmospheres. Natural gas—called a fossil fuel because it is formed from the decomposition of plant and animal material in the Earth's crust—is approximately 75% methane.

You may be surprised to learn that carbon forms four covalent bonds, since you know that carbon has only two unpaired valence electrons (Table 1.2). But if carbon formed only two covalent bonds, it would not complete its octet. We need, therefore, to come up with an explanation that accounts for the observation that carbon forms four covalent bonds and has a complete octet.

If one of the electrons in carbon's 2*s* orbital were promoted into its empty 2*p* orbital, then carbon would have four unpaired valence electrons (in which case four covalent bonds could be formed).

However, we have seen that the four C—H bonds in methane are identical. How can they be identical if carbon uses an *s* orbital and three *p* orbitals to form these four bonds? Wouldn't the bond formed with the *s* orbital be different from the three bonds formed with *p* orbitals? The four C—H bonds are identical because carbon uses hybrid atomic orbitals.

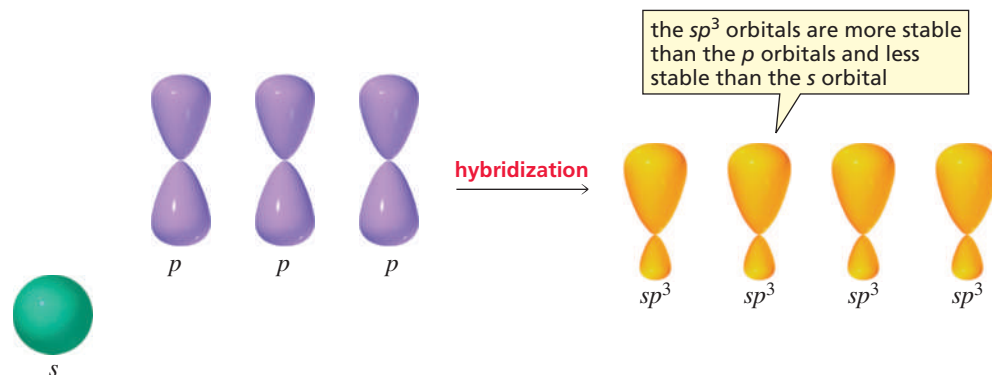
Hybrid orbitals result from combining atomic orbitals.

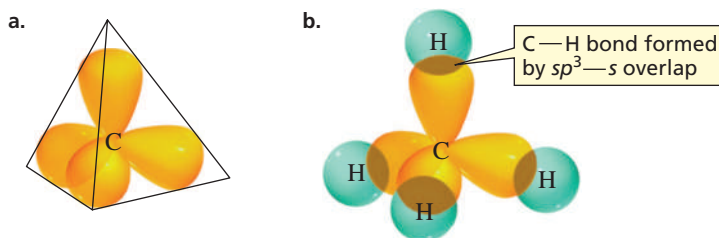
Hybrid orbitals are mixed orbitals that result from combining atomic orbitals. The concept of combining atomic orbitals, called **hybridization,** was first proposed by Linus Pauling in 1931.

If the one *s* and three *p* orbitals of the second shell are all combined and then apportioned into four equal orbitals, each of the four resulting orbitals will be one part *s* and three parts *p*. This type of mixed orbital is called an sp^3 (read "*s*-*p*-three," not "*s*-*p*-cubed") orbital. (The superscript 3 means that three *p* orbitals were mixed with one *s* orbital—the superscript 1 on the *s* is implied—to form the four hybrid orbitals.) Each sp^3 orbital has 25% *s* character and 75% *p* character. Each of the four sp^3 orbitals has the same energy.

Like a *p* orbital, an sp^3 orbital has two lobes. Unlike those of an sp^3 orbital, however, the lobes differ in size (Figure 1.3). The larger lobe of the sp^3 orbital is used to form covalent bonds.

Figure 1.3
An *s* orbital and three *p* orbitals hybridize to form four sp^3 orbitals. An sp^3 orbital is more stable (lower in energy) than a *p* orbital, but less stable (higher in energy) than an *s* orbital.

Electron pairs stay as far from each other as possible.

The four sp^3 orbitals adopt a spatial arrangement that keeps them as far away from each other as possible. They do this because electrons repel each other, and moving as far from each other as possible minimizes the repulsion.

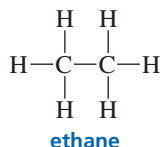
When four sp^3 orbitals move as far from each other as possible, they point toward the corners of a regular tetrahedron—a pyramid with four faces, each an equilateral triangle (Figure 1.4a). Each of the four C—H bonds in methane is formed from the overlap of an sp^3 orbital of carbon with the *s* orbital of a hydrogen (Figure 1.4b). This explains why the four C—H bonds are identical.

◀ **Figure 1.4**
(a) The four sp^3 orbitals are directed toward the corners of a tetrahedron, causing each bond angle to be 109.5°. This arrangement allows the four orbitals to be as far apart as possible.
(b) An orbital picture of methane, showing the overlap of each sp^3 orbital of carbon with the *s* orbital of a hydrogen. (For clarity, the smaller lobes of the sp^3 orbitals are not shown.)

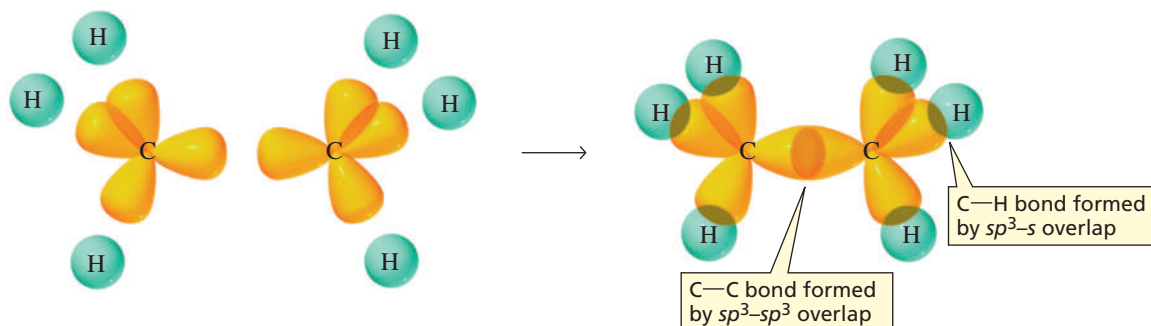
The angle between any two lines that point from the center to the corners of a tetrahedron is 109.5°. The bond angles in methane, therefore, are 109.5°. This is called a **tetrahedral bond angle.** A carbon atom, such as the one in methane, that forms covalent bonds using four equivalent sp^3 orbitals is called a **tetrahedral carbon.**

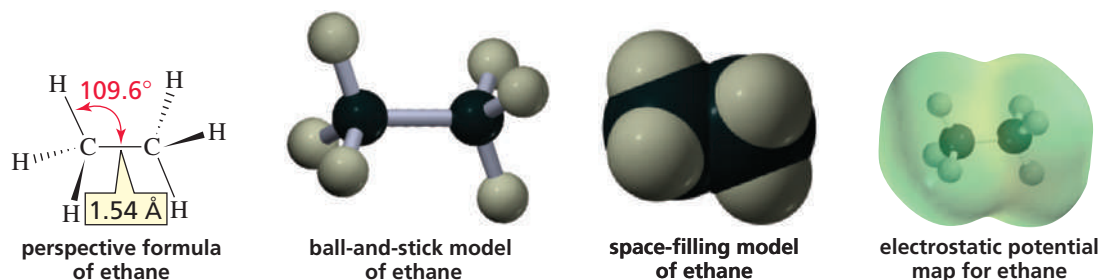
If you are thinking that hybrid orbital theory appears to have been contrived just to make things fit, then you are right. Nevertheless, it gives us a very good picture of the bonding in organic compounds.

The Bonds in Ethane

Each carbon in ethane (CH_3CH_3) is bonded to four other atoms. Thus, both carbons are tetrahedral.

```
    H   H
    |   |
H — C — C — H
    |   |
    H   H
```
ethane

One bond connecting two atoms is called a **single bond.** All the bonds in ethane are single bonds.

Each carbon uses four sp^3 orbitals to form the four covalent bonds (Figure 1.5). One sp^3 orbital of one carbon of ethane overlaps an sp^3 orbital of the other carbon to form the C—C bond.

▲ **Figure 1.5**
An orbital picture of ethane. The C—C bond is formed by sp^3–sp^3 overlap, and each C—H bond is formed by sp^3–*s* overlap. (The smaller lobes of the sp^3 orbitals are not shown.) As a result, both carbons are tetrahedral and all bond angles are ~109.5°.

The three remaining sp^3 orbitals of each carbon overlap the *s* orbital of a hydrogen to form a C—H bond. Thus, the C—C bond is formed by sp^3–sp^3 overlap, and each C—H bond is formed by sp^3–*s* overlap. Each of the bond angles in ethane is nearly the tetrahedral bond angle of 109.5°, and the length of the C—C bond is 1.54 Å. The potential map shows that ethane, like methane, is a nonpolar molecule.

All the bonds in methane and ethane are sigma (σ) bonds. We will see that all *single bonds* in organic compounds are *sigma bonds*.

All single bonds found in organic compounds are sigma bonds.

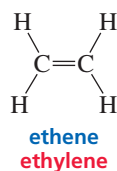
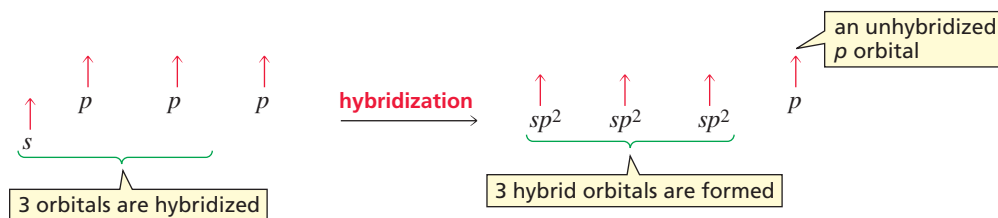
PROBLEM 19♦

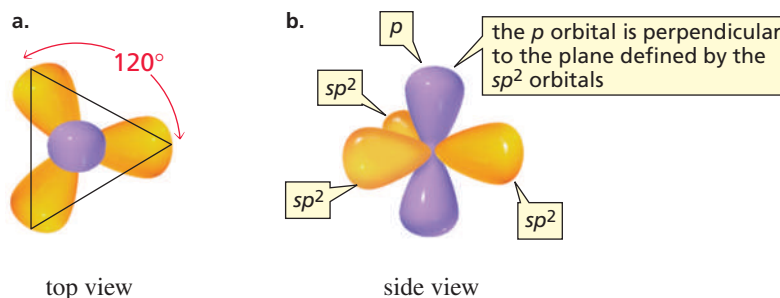
What orbitals are used to form the 10 sigma bonds in propane ($CH_3CH_2CH_3$)?

1.8 HOW A DOUBLE BOND IS FORMED: THE BONDS IN ETHENE

Each of the carbon atoms in ethene (also called ethylene) forms four bonds, but each carbon is bonded to only three atoms:

$H_2C{=}CH_2$

ethene
ethylene

To bond to three atoms, each carbon hybridizes three atomic orbitals: an *s* orbital and two of the *p* orbitals. Because three orbitals are hybridized, three hybrid orbitals are formed. These are called sp^2 orbitals. After hybridization, each carbon atom has three sp^2 orbitals and one unhybridized *p* orbital:

To minimize electron repulsion, the three sp^2 orbitals need to get as far from each other as possible. Therefore, the axes of the three orbitals lie in a plane. As a result, the bond angles are all close to 120° (Figure 1.6a). The unhybridized *p* orbital is perpendicular to the plane defined by the axes of the sp^2 orbitals (Figure 1.6b).

▶ **Figure 1.6**
(a) The three sp^2 orbitals lie in a plane, oriented 120° from each other. (The smaller lobes of the sp^2 orbitals are not shown.)
(b) The unhybridized *p* orbital is perpendicular to this plane.

The carbons in ethene form two bonds with each other. Two bonds connecting two atoms is called a **double bond.** The two carbon–carbon bonds in the double bond are not identical. One of them results from the overlap of an sp^2 orbital of one carbon with an sp^2 orbital of the other carbon; this is a sigma (σ) bond. Each carbon uses its other two sp^2 orbitals to overlap the s orbital of a hydrogen to form the C—H bonds (Figure 1.7a).

The second carbon–carbon bond results from side-to-side overlap of the two unhybridized p orbitals. Side-to-side overlap of p orbitals forms a **pi (π) bond** (Figure 1.7b). Thus, one of the bonds in a double bond is a σ bond, and the other is a π bond. All the C—H bonds are σ bonds. (Remember that all single bonds in organic compounds are σ bonds.)

A double bond consists of one σ bond and one π bond.

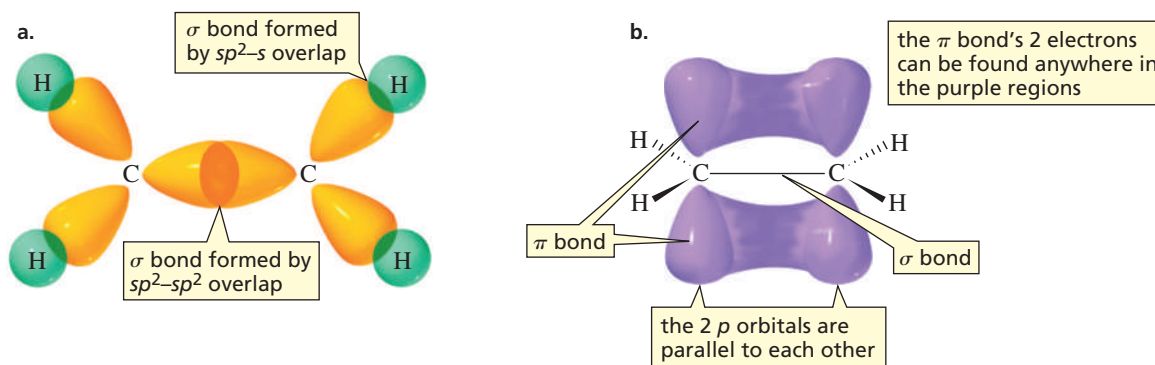



Figure 1.7

(a) One C—C bond in ethene (looking down from the top) is a σ bond formed by sp^2–sp^2 overlap, and the C—H bonds are σ bonds formed by sp^2–s overlap.

(b) The second C—C bond (looking from the side) is a π bond formed by side-to-side overlap of a p orbital of one carbon with a p orbital of the other carbon. The two p orbitals are parallel to each other.

For maximum overlap to occur, the two p orbitals that overlap to form the π bond must be parallel to each other (Figure 1.7b). This forces the triangle formed by one carbon and two hydrogens to lie in the same plane as the triangle formed by the other carbon and two hydrogens. As a result, all six atoms of ethene lie in the same plane, and the electrons in the p orbitals occupy a volume of space above and below the plane (Figure 1.8).

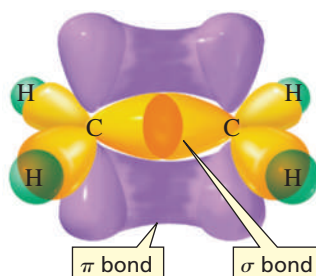



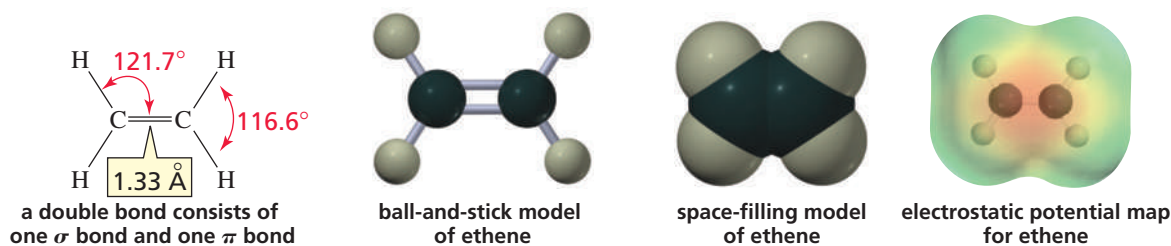
Figure 1.8
The two carbons and four hydrogens lie in the same plane. Perpendicular to that plane are the two parallel p orbitals. This results in an accumulation of electron density above and below the plane containing the two carbons and four hydrogens.

The potential map for ethene shows that it is a nonpolar molecule with a slight accumulation of negative charge (the pale orange area) above the two carbons. (If you could turn the potential map over, you would find a similar accumulation of negative charge on the other side.)

a double bond consists of one σ bond and one π bond

ball-and-stick model of ethene

space-filling model of ethene

electrostatic potential map for ethene

Four electrons hold the carbons together in a carbon–carbon double bond, but only two electrons hold the carbons together in a carbon–carbon single bond. This means that a carbon–carbon double bond is stronger and shorter than a carbon–carbon single bond.

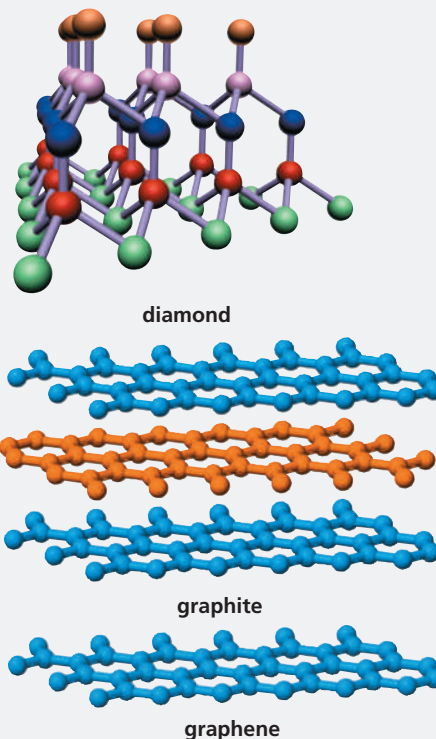
Diamond, Graphite, Graphene, and Fullerenes: Substances that Contain Only Carbon Atoms

The difference that hybridization can make is illustrated by diamond and graphite. Diamond is the hardest of all substances, whereas graphite is a slippery, soft solid most familiar to us as the "lead" in pencils. Both materials, in spite of their very different physical properties, contain only carbon atoms. The two substances differ solely in the hybridization of the carbon atoms.

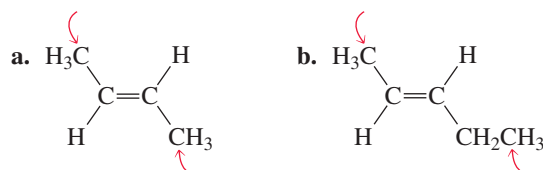
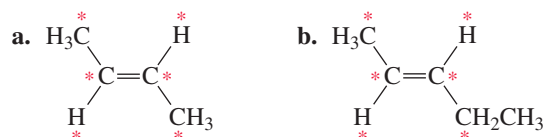
Diamond consists of a rigid three-dimensional network of carbon atoms, with each carbon bonded to four others via sp^3 orbitals.

The carbon atoms in graphite, on the other hand, are sp^2 hybridized, so each bonds to only three other carbons. This trigonal planar arrangement causes the atoms in graphite to lie in flat, layered sheets. Since there are no covalent bonds between the sheets, they can shear off from neighboring sheets.

Diamond and graphite have been known since ancient times—but a third substance that contains only carbon atoms was discovered just 8 years ago. Graphene is a one-atom-thick planar sheet of graphite. It is the thinnest and lightest material known. It is transparent and can be bent, stacked, or rolled. It is harder than diamond and it conducts electricity better than copper.

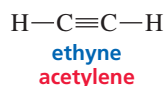
Fullerenes are also naturally occurring compounds that contain only carbon. Like graphite and graphene, fullerenes consist solely of sp^2 carbons, but instead of forming planar sheets, the carbons join to form spherical structures. (Fullerenes are discussed further in Section 7.15.)

PROBLEM 20 Solved

Do the sp^2 carbons and the indicated sp^3 carbons have to lie in the same plane?

a. H_3C(H)C=C(H)CH_3 **b.** H_3C(H)C=C(H)CH_2CH_3

Solution The two sp^2 carbons and the atoms that are bonded to each of the sp^2 carbons all lie in the same plane. The other atoms in the molecule will not lie in the same plane as these six atoms. By putting stars on the six atoms that do lie in the same plane, you will be able to see if the indicated atoms lie in the same plane. They are in the same plane in part **a,** but they are not necessarily in the same plane in part **b.**

Oxyacetylene torches are used to weld and cut metals. The torch uses acetylene and mixes it with oxygen to increase the temperature of the flame. An acetylene/oxygen flame burns at ~3500 °C.

1.9 HOW A TRIPLE BOND IS FORMED: THE BONDS IN ETHYNE

Each of the carbon atoms in ethyne (also called acetylene) forms four bonds, but each carbon is bonded to only two atoms—a hydrogen and another carbon:

$$H{-}C{\equiv}C{-}H$$

ethyne
acetylene

In order to bond to two atoms, each carbon hybridizes two atomic orbitals—an *s* and a *p*. Two identical *sp* orbitals result.

▲ **Figure 1.9**
The two *sp* orbitals point in opposite directions. The two unhybridized *p* orbitals are perpendicular to each other and to the *sp* orbitals. (The smaller lobes of the *sp* orbitals are not shown.)

Each carbon atom in ethyne, therefore, has two *sp* orbitals and two unhybridized *p* orbitals. To minimize electron repulsion, the two *sp* orbitals point in opposite directions (Figure 1.9).

The two carbons in ethyne are held together by three bonds. Three bonds connecting two atoms is called a **triple bond.** One of the *sp* orbitals of one carbon in ethyne overlaps an *sp* orbital of the other carbon to form a carbon–carbon σ bond. The other *sp* orbital of each carbon overlaps the *s* orbital of a hydrogen to form a C—H σ bond (Figure 1.10a). Because the two *sp* orbitals point in opposite directions, the bond angles are 180°.

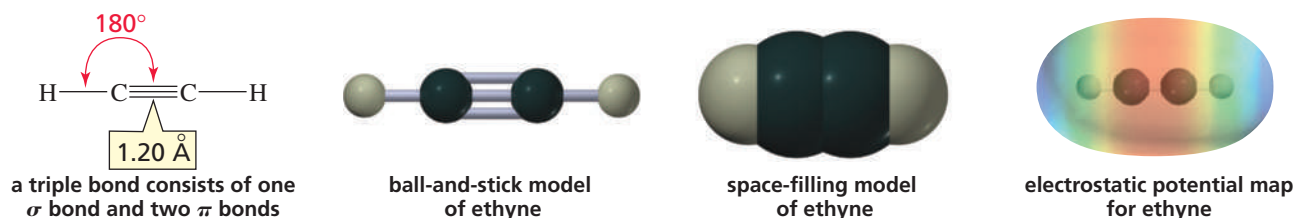
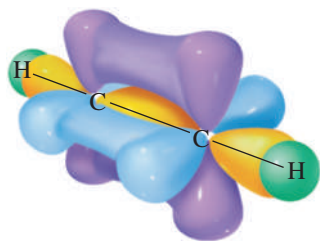
Each of the unhybridized *p* orbitals engages in side-to-side overlap with a parallel *p* orbital on the other carbon, resulting in the formation of two π bonds (Figure 1.10b).

▲ **Figure 1.10**
(a) The C—C σ bond in ethyne is formed by *sp*–*sp* overlap, and the C—H bonds are formed by *sp*–*s* overlap. The carbon atoms and the atoms bonded to them form a straight line.
(b) The two carbon–carbon π bonds are formed by side-to-side overlap of the two *p* orbitals of one carbon with the two *p* orbitals of the other carbon.

Thus, a triple bond consists of one σ bond and two π bonds. Because the two unhybridized *p* orbitals on each carbon are perpendicular to each other, they create regions of high electron density above and below *and* in front of and in the back of the internuclear axis of the molecule (Figure 1.11).

A triple bond consists of one σ bond and two π bonds.

The overall result can be seen in the potential map for ethyne—the negative charge accumulates in a cylinder that wraps around the egg-shaped molecule.

a triple bond consists of one σ bond and two π bonds | ball-and-stick model of ethyne | space-filling model of ethyne | electrostatic potential map for ethyne

▲ **Figure 1.11**
The triple bond has an electron-dense region above and below and in front of and in the back of the internuclear axis of the molecule.

The two carbon atoms in a triple bond are held together by six electrons, so a triple bond is stronger and shorter than a double bond.

PROBLEM 21

Put a number in each of the blanks:

a. ___ *s* orbital and ___ *p* orbitals form ____ sp^3 orbitals.

b. ___ *s* orbital and ___ *p* orbitals form ____ sp^2 orbitals.

c. ___ *s* orbital and ___ *p* orbitals form ____ *sp* orbitals.

PROBLEM 22 Solved

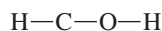
For each of the given species:

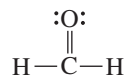
a. Draw its Lewis structure.

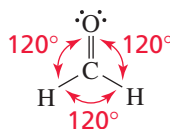
b. Describe the orbitals used by each carbon atom in bonding and indicate the approximate bond angles.

1. H_2CO **2.** CCl_4 **3.** CH_3CO_2H **4.** HCN

Solution to 22a1 Our first attempt at a Lewis structure (drawing the atoms with the hydrogens on the outside of the molecule) shows that carbon is the only atom that does not form the needed number of bonds.

H—C—O—H

If we place a double bond between carbon and oxygen and move the H from O to C (which still keeps the Hs on the outside of the molecule), then all the atoms end up with the correct number of bonds. Lone-pair electrons are used to give oxygen a filled outer shell. When we check to see if any atom needs to be assigned a formal charge, we find that none of them does.

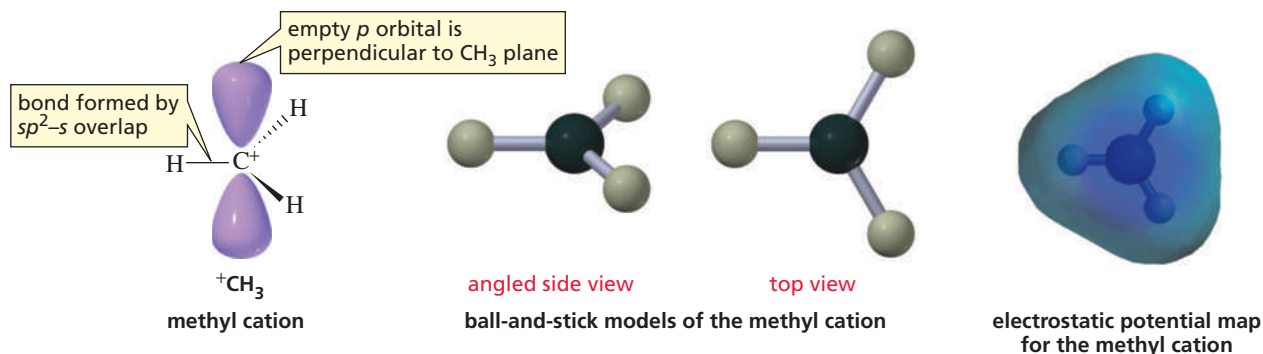
:O:
‖
H—C—H

Solution to 22b1 Because carbon forms a double bond, we know that it uses sp^2 orbitals (as it does in ethene) to bond to the two hydrogens and the oxygen. It uses its "left-over" *p* orbital to form the second bond to oxygen. Because carbon is sp^2 hybridized, the bond angles are approximately 120°.

:O:
120° ‖ 120°
C
H 120° H

1.10 THE BONDS IN THE METHYL CATION, THE METHYL RADICAL, AND THE METHYL ANION

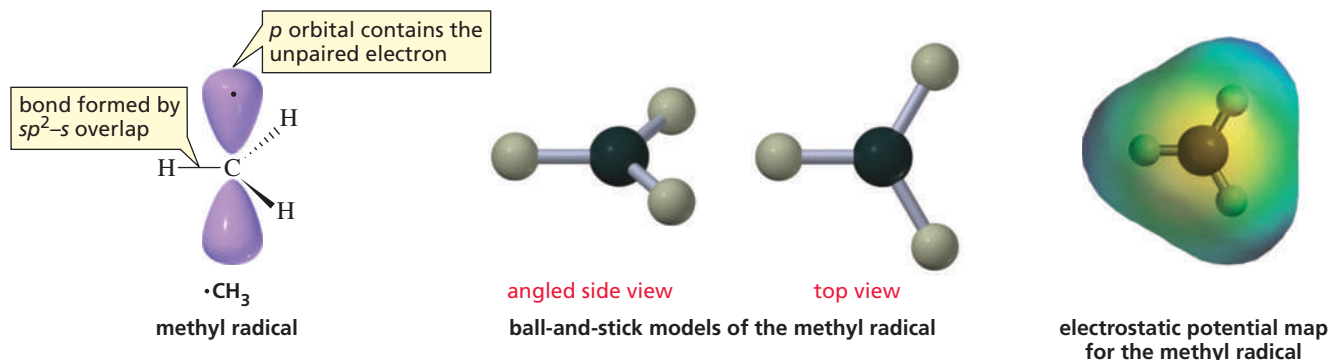
Not all carbon atoms form four bonds. A carbon with a positive charge, a negative charge, or an unpaired electron forms only three bonds. Now we will see what orbitals carbon uses when it forms three bonds.

The Methyl Cation ($^+CH_3$)

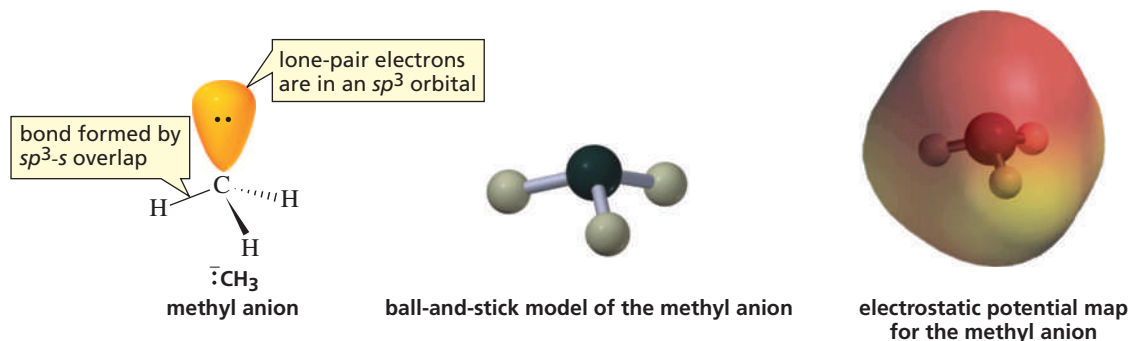
The carbon in $^+CH_3$ is sp^2 hybridized.

The positively charged carbon in the methyl cation is bonded to three atoms, so it hybridizes three orbitals—an *s* orbital and two *p* orbitals. Therefore, it forms its three covalent bonds using sp^2 orbitals. Its unhybridized *p* orbital remains empty. The positively charged carbon, and the three atoms bonded to it, lie in a plane. The unhybridized *p* orbital stands perpendicular to the plane.

The Methyl Radical ($\cdot CH_3$)

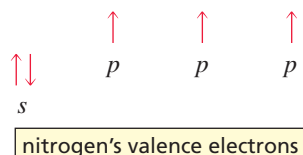
The carbon atom in the methyl radical is also sp^2 hybridized. The methyl radical, though, has one more electron than the methyl cation. That electron is unpaired and it resides in the *p* orbital, with half of the electron density in each lobe. Although the methyl cation and the methyl radical have similar ball-and-stick models, the potential maps are quite different because of the additional electron in the methyl radical.

The carbon in $\cdot CH_3$ is sp^2 hybridized.

The Methyl Anion ($\ddot{:}CH_3^-$)

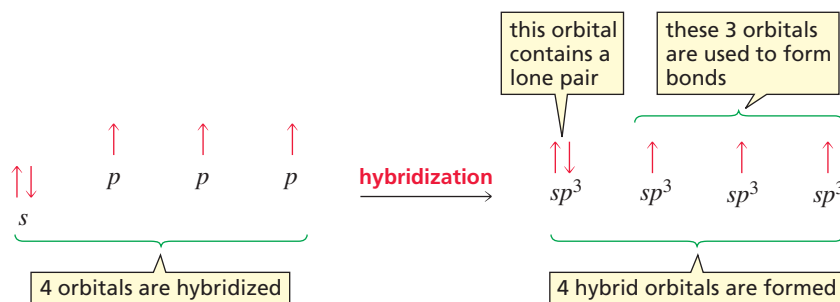
The negatively charged carbon in the methyl anion has three pairs of bonding electrons and one lone pair. Four pairs of electrons are farthest apart when the four orbitals containing the bonding and lone-pair electrons point toward the corners of a tetrahedron. Thus, a negatively charged carbon is sp^3 hybridized. In the methyl anion, three of carbon's sp^3 orbitals each overlap the *s* orbital of a hydrogen, and the fourth sp^3 orbital holds the lone pair.

The carbon in $:CH_3^-$ is sp^3 hybridized.

Take a moment to compare the potential maps for the methyl cation, the methyl radical, and the methyl anion.

1.11 THE BONDS IN AMMONIA AND IN THE AMMONIUM ION

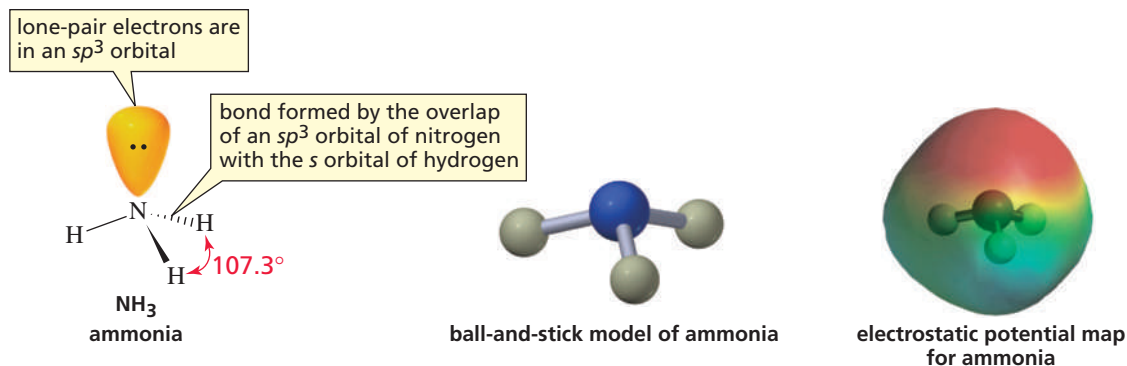
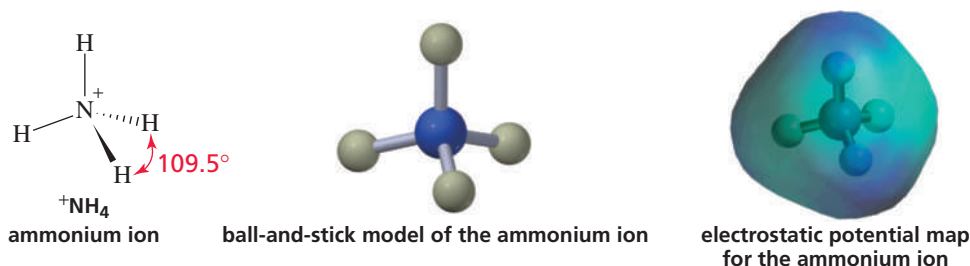
The nitrogen atom in ammonia (NH_3) forms three covalent bonds. Nitrogen's electronic configuration shows that it has three unpaired valence electrons (Table 1.2), so it does not need to promote an electron to form the three covalent bonds required to achieve an outer shell of eight electrons—that is, to complete its octet.

However, this simple picture presents a problem. If nitrogen uses *p* orbitals to form the three N—H bonds, as predicted by its electronic configuration, then we would expect bond angles of about 90° because the three *p* orbitals are at right angles to each other. But the experimentally observed bond angles in NH_3 are 107.3°.

The observed bond angles can be explained if we assume that nitrogen uses hybrid orbitals to form covalent bonds—just as carbon does. The *s* orbital and three *p* orbitals hybridize to form four degenerate sp^3 orbitals.

The bond angles in a molecule indicate which orbitals are used in bond formation.

Each of the three N—H bonds in NH_3 is formed from the overlap of an sp^3 orbital of nitrogen with the *s* orbital of a hydrogen. The lone pair occupies the fourth sp^3 orbital. The observed bond angle (107.3°) is a little smaller than the tetrahedral bond angle (109.5°) because of the lone pair. A lone pair is more diffuse than a bonding pair that is shared by two nuclei and relatively confined between them. Consequently, a lone pair exerts more electron repulsion, causing the N—H bonds to squeeze closer together, which decreases the bond angle.

NH_3
ammonia

ball-and-stick model of ammonia

electrostatic potential map for ammonia

Because the ammonium ion ($^+NH_4$) has four identical N—H bonds and no lone pairs, all the bond angles are 109.5°, just like the bond angles in methane.

Take a moment to compare the potential maps for ammonia and the ammonium ion.

PROBLEM 23♦

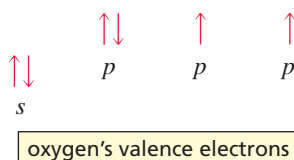
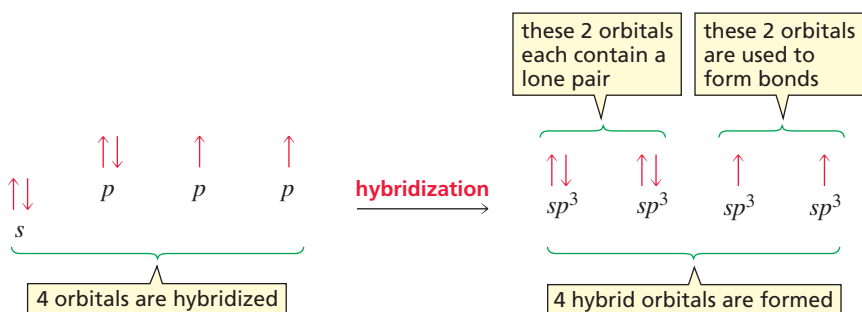
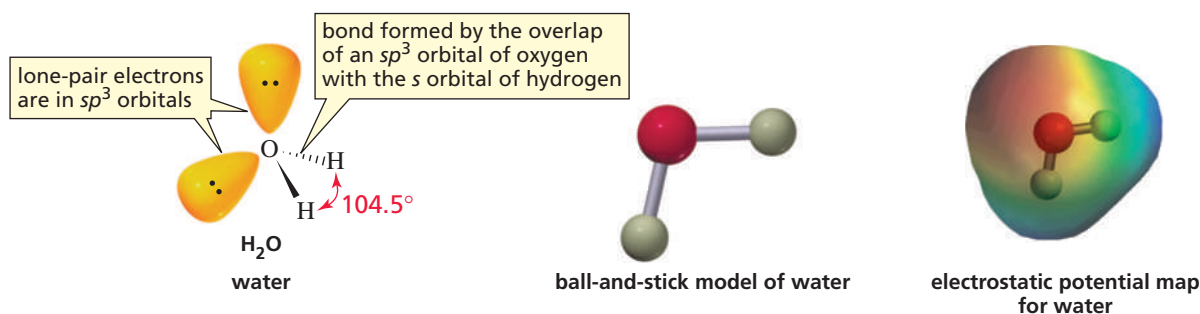
Predict the approximate bond angles in

a. the methyl cation. **b.** the methyl radical. **c.** the methyl anion.

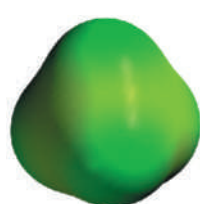
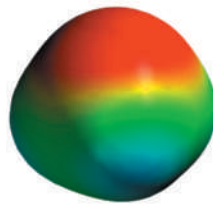
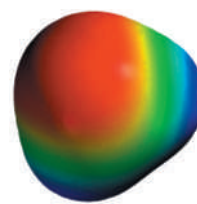
PROBLEM 24♦

According to the potential map for the ammonium ion, which atom has the greatest electron density?

1.12 THE BONDS IN WATER

The oxygen atom in water (H_2O) forms two covalent bonds. Because oxygen's electronic configuration shows that it has two unpaired valence electrons, oxygen does not need to promote an electron to form the two covalent bonds required to complete its octet.

The experimentally observed bond angle in H_2O is 104.5°. The bond angle indicates that oxygen, like carbon and nitrogen, uses hybrid orbitals when it forms covalent bonds. Also like carbon and nitrogen, the one *s* and three *p* orbitals hybridize to form four degenerate sp^3 orbitals:

Each of the two O—H bonds is formed by the overlap of an sp^3 orbital of oxygen with the *s* orbital of a hydrogen. A lone pair occupies each of the two remaining sp^3 orbitals.

The bond angle in water (104.5°) is even smaller than the bond angles in NH_3 (107.3°) because oxygen has two relatively diffuse lone pairs, whereas nitrogen has only one.

PROBLEM 25♦

Compare the potential maps for methane, ammonia, and water. Which is the most polar molecule? Which is the least polar?

electrostatic potential map for methane

electrostatic potential map for ammonia

electrostatic potential map for water

PROBLEM 26 Solved

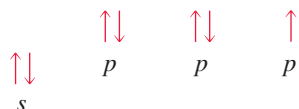
The bond angles in H_3O^+ are less than ________ and greater than ________.

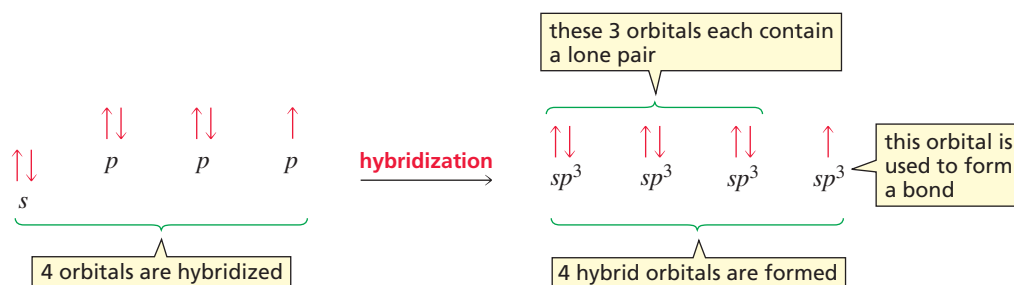
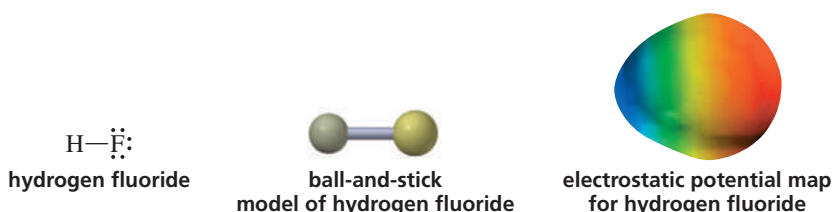
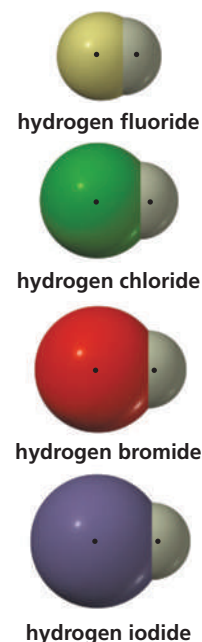
Solution The carbon atom in CH_4 has no lone pairs; its bond angles are 109.5°. The oxygen atom in H_3O^+ has one lone pair. A lone pair is more diffuse than a bonding pair, so the O—H bonds squeeze together to minimize electron repulsion. However, they do not squeeze as closely together as they do in water (104.5°), where oxygen has two lone pairs. Therefore, the bond angles in H_3O^+ are less than 109.5° and greater than 104.5°.

Water—A Compound Central to Life

Water is the most abundant compound found in living organisms. Its unique properties have allowed life to originate and evolve. For example, its high heat of fusion (the heat required to convert a solid to a liquid) protects organisms from freezing at low temperatures because a lot of heat must be removed from water to freeze it. Its high heat capacity (the heat required to raise the temperature of a substance by a given amount) minimizes temperature changes in organisms, and its high heat of vaporization (the heat required to convert a liquid to a gas) allows animals to cool themselves with a minimal loss of body fluid. Because liquid water is denser than ice, ice formed on the surface of water floats and insulates the water below. That is why oceans and lakes freeze from the top down (not from the bottom up) and why plants and aquatic animals can survive when the ocean or lake they live in freezes.

1.13 THE BOND IN A HYDROGEN HALIDE

HF, HCl, HBr, and HI are called hydrogen halides. A halogen has only one unpaired valence electron (Table 1.2), so it forms only one covalent bond.

Bond angles will not help us determine the orbitals that form the hydrogen halide bond, as they did with other molecules, because hydrogen halides have only one bond

and therefore no bond angles. We do know, however, that a halogen's three lone pairs are energetically identical and that lone-pair electrons position themselves to minimize electron repulsion. Both of these observations suggest that the halogen's three lone pairs are in sp^3 orbitals.

Therefore, we will assume that the hydrogen–halogen bond is formed by the overlap of an sp^3 orbital of the halogen with the *s* orbital of hydrogen.

In the case of fluorine, the sp^3 orbital used in bond formation belongs to the second shell of electrons. In chlorine, the sp^3 orbital belongs to the third shell. Because the average distance from the nucleus is greater for an electron in the third shell than it is for an electron in the second shell, the average electron density is less in a $3sp^3$ orbital than it is in a $2sp^3$ orbital. This means that the electron density in the region where the *s* orbital of hydrogen overlaps the sp^3 orbital of the halogen decreases as the size of the halogen increases (Figure 1.12). Therefore, the hydrogen–halogen bond becomes longer and weaker as the size (atomic weight) of the halogen increases (Table 1.6).

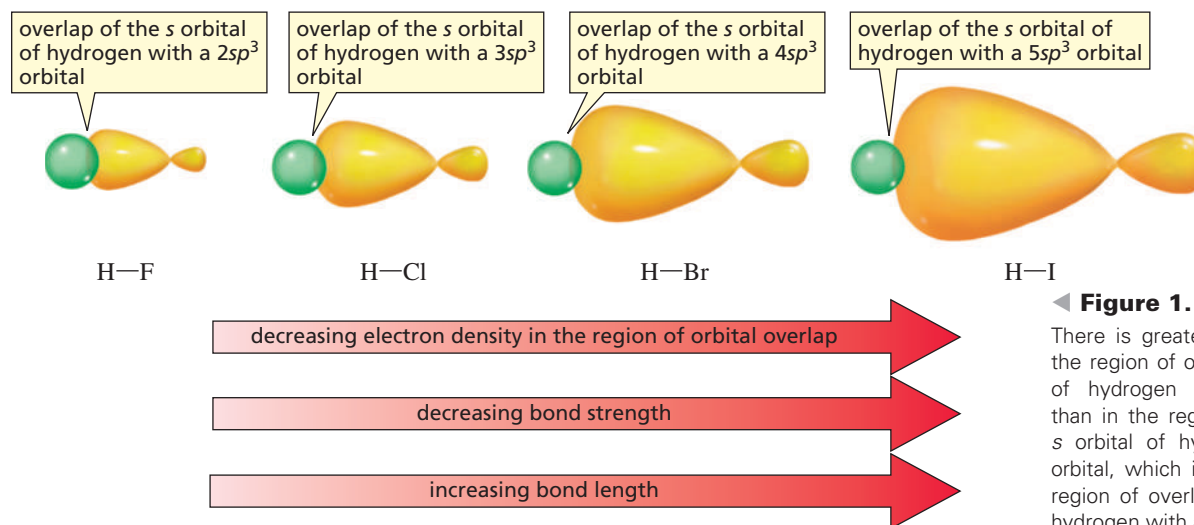



Figure 1.12
There is greater electron density in the region of overlap of the *s* orbital of hydrogen with a $2sp^3$ orbital than in the region of overlap of the *s* orbital of hydrogen with a $3sp^3$ orbital, which is greater than in the region of overlap of the *s* orbital of hydrogen with a $4sp^3$ orbital.

Table 1.6 Hydrogen–Halogen Bond Lengths and Bond Strengths

Hydrogen halide	Bond length (Å)	Bond strength (kcal/mol)	(kJ/mol)
H—F	0.917	136	571
H—Cl	1.275	103	432
H—Br	1.415	87	366
H—I	1.609	71	298

The hydrogen–halogen bond becomes longer and weaker as the size of the halogen increases.

PROBLEM 27♦

a. Predict the relative lengths and strengths of the bonds in Cl_2 and Br_2.

b. Predict the relative lengths and strengths of the carbon–halogen bonds in CH_3F, CH_3Cl, and CH_3Br.

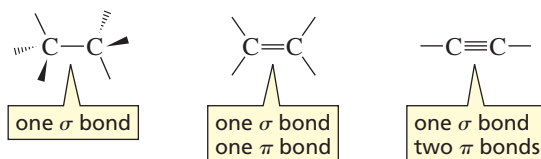
PROBLEM 28♦

a. Which bond would be longer? **b.** Which bond would be stronger?

1. C—Cl or C—I **2.** C—C or C—Cl **3.** H—Cl or H—F

1.14 SUMMARY: HYBRIDIZATION, BOND LENGTHS, BOND STRENGTHS, AND BOND ANGLES

We have seen that all *single bonds* are σ bonds, all double bonds are composed of one σ bond and one π bond, and all triple bonds are composed of one σ bond and two π bonds.

C—C: one σ bond
C=C: one σ bond, one π bond
—C≡C—: one σ bond, two π bonds

The hybridization of a C, N, or O is $sp^{(3 \text{ minus the number of } \pi \text{ bonds})}$.

The easiest way to determine the hybridization of carbon, nitrogen, or oxygen is to count the number of π bonds it forms. If it forms no π bonds, it is sp^3 hybridized; if it forms one π bond, it is sp^2 hybridized; and if it forms two π bonds, it is *sp* hybridized. The exceptions are carbocations and carbon radicals, which are sp^2 hybridized—not because they form a π bond, but because they have an empty or a half-filled *p* orbital (Section 1.10).

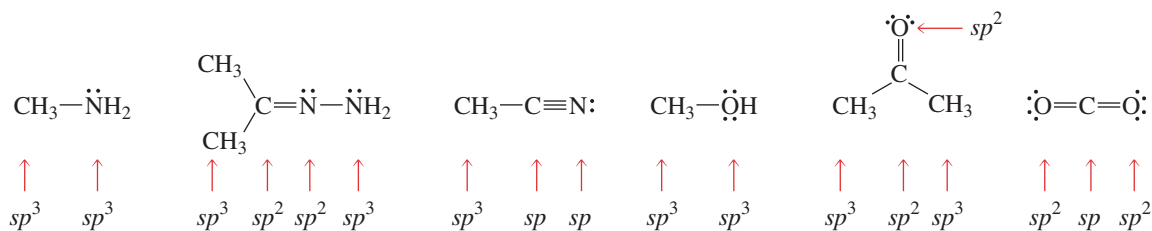
CH_3—$\ddot{N}H_2$: sp^3, sp^3

$(CH_3)_2C$=$\ddot{N}$—$\ddot{N}H_2$: sp^3, sp^2, sp^2, sp^3

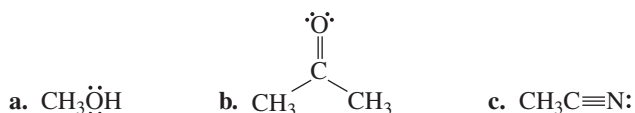
CH_3—C≡N: : sp^3, sp, sp

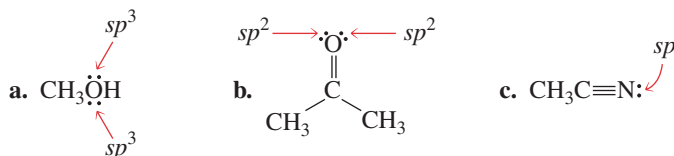
CH_3—$\ddot{O}H$: sp^3, sp^3

$CH_3C(=\ddot{O})CH_3$: sp^3, sp^2, sp^3; O ← sp^2

:Ö=C=Ö: : sp^2, sp, sp^2

PROBLEM 29 Solved

In what orbitals are the lone pairs in each of the following molecules?

a. $CH_3\ddot{O}H$ **b.** $CH_3C(=\ddot{O})CH_3$ **c.** $CH_3C{\equiv}N:$

Solution

a. Oxygen forms only single bonds in this compound, so it is *sp*^{3} hybridized. It uses two of its four *sp*^{3} orbitals to form σ bonds (one to C and one to H) and the other two for its lone pairs.

b. Oxygen forms a double bond in this compound, so it is *sp*^{2} hybridized. It uses one of its three *sp*^{2} orbitals to form the σ bond to C and the other two for its lone pairs.

c. Nitrogen forms a triple bond in this compound, so it is *sp* hybridized. It uses one of the *sp* orbitals to form the σ bond to C and the other one for its lone pair.

Ethane

Ethene

Ethyne

In comparing the lengths and strengths of carbon–carbon single, double, and triple bonds, we see that the carbon–carbon bond gets shorter and stronger as the number of bonds holding the two carbon atoms together increases (Table 1.7). As a result, triple bonds are shorter and stronger than double bonds, which are shorter and stronger than single bonds.

bond strength decreases as bond length increases

The greater the electron density in the region of overlap, the stronger the bond.

The shorter the bond, the stronger it is.

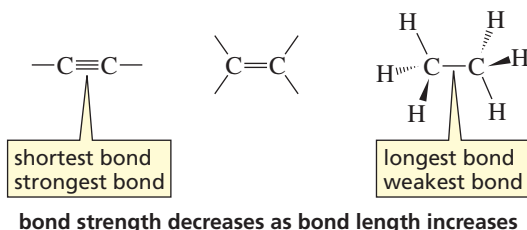
A π bond is weaker than a σ bond.

From Table 1.7 we see that a double bond (a σ bond plus a π bond) is stronger (174 kcal/mol) than a single bond (a σ bond; 90 kcal/mol), but it is not twice as strong, so we can conclude that the π bond of a double bond is weaker than the σ bond.

Table 1.7 Comparison of the Bond Angles and the Lengths and Strengths of the Carbon–Carbon and Carbon–Hydrogen Bonds in Ethane, Ethene, and Ethyne

Molecule	Hybridization of carbon	Bond angles	Length of C—C bond (Å)	Strength of C—C bond (kcal/mol)	(kJ/mol)	Length of C—H bond (Å)	Strength of C—H bond (kcal/mol)	(kJ/mol)
$H_3C{-}CH_3$ ethane	*sp*^{3}	109.5°	1.54	90.2	377	1.10	101.1	423
$H_2C{=}CH_2$ ethene	*sp*^{2}	120°	1.33	174.5	730	1.08	110.7	463
$H{-}C{\equiv}C{-}H$ ethyne	*sp*	180°	1.20	230.4	964	1.06	133.3	558

You may wonder how an electron "knows" what orbital it should go into. In fact, electrons know nothing about orbitals. They simply occupy the space around atoms in the most stable arrangement possible. It is chemists who use the concept of orbitals to explain this arrangement.

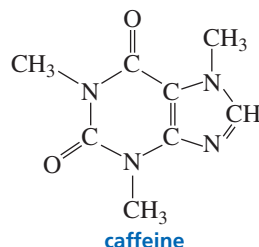
coffee beans

PROBLEM 30♦

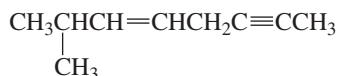
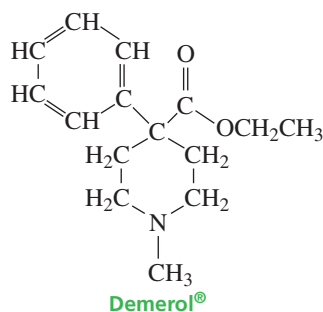
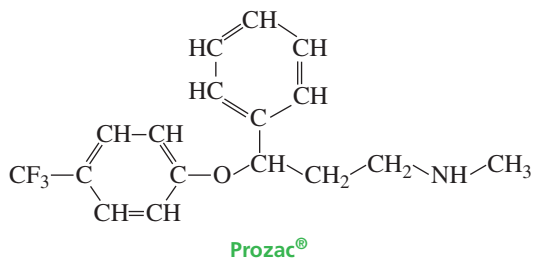
Which of the bonds in a carbon–oxygen double bond has more effective orbital–orbital overlap, the σ bond or the π bond?

PROBLEM 31

Caffeine is a natural insecticide, found in the seeds and leaves of certain plants, where it kills insects that feed on the plant. Caffeine is extracted for human consumption from beans of the coffee plant, from Kola nuts, and from the leaves of tea plants. Because it stimulates the central nervous system, it temporarily prevents drowsiness. Add caffeine's missing lone pairs to its structure.

caffeine

PROBLEM 32

a. What is the hybridization of each of the carbon atoms in the following compound?

$$CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH{=}CHCH_2C{\equiv}CCH_3$$

b. What is the hybridization of each of the atoms in Demerol and Prozac?

Demerol®
used to treat moderate to severe pain

Prozac®
used to treat depression, obsessive-compulsive disorder, some eating disorders, and panic attacks

PROBLEM-SOLVING STRATEGY

Predicting Bond Angles

Predict the approximate bond angle of the C—N—H bond in $(CH_3)_2NH$.

First we need to determine the hybridization of the central atom (the N). Because the nitrogen atom forms only single bonds, we know it is sp^3 hybridized. Next, we look to see if there are lone pairs that will affect the bond angle. An uncharged nitrogen has one lone pair. Based on these observations, we can predict that the C—N—H bond angle will be about 107.3°, the same as the H—N—H bond angle in NH_3, which is another compound with an sp^3 nitrogen and one lone pair.

Now use the strategy you have just learned to solve Problem 33.

PROBLEM 33♦

Predict the approximate bond angles for

a. the C—N—C bond angle in $(CH_3)_2\overset{+}{N}H_2$.
b. the C—N—H bond angle in $CH_3CH_2NH_2$.
c. the H—C—N bond angle in $(CH_3)_2NH$.
d. the H—C—O bond angle in CH_3OCH_3.

PROBLEM 34

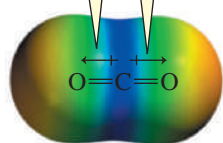
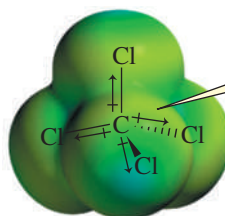
Describe the orbitals used in bonding and the bond angles in the following compounds:

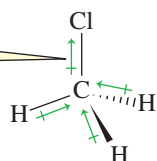
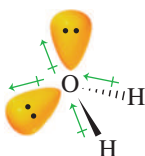
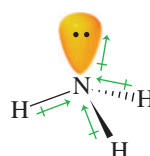
a. CCl_4 **b.** CH_3OH **c.** HCOOH **d.** N_2

1.15 THE DIPOLE MOMENTS OF MOLECULES

In Section 1.3, we saw that if a molecule has one covalent bond, then the dipole moment of the molecule is identical to the dipole moment of the bond. When molecules have more than one covalent bond, the geometry of the molecule must be taken into account because both the *magnitude* and the *direction* of the individual bond dipole moments (the vector sum) determine the overall dipole moment of the molecule.

The dipole moment depends on the magnitude of the individual bond dipoles and the direction of the individual bond dipoles.

Because the direction of the bond dipoles has to be taken into account, totally symmetrical molecules have no dipole moment. In carbon dioxide (CO_2), for example, the carbon is bonded to two atoms, so it uses *sp* orbitals to form the two C—O σ bonds. The remaining two *p* orbitals on the carbon form the two C—O π bonds. The *sp* orbitals form a bond angle of 180°, which causes the individual carbon–oxygen bond dipole moments to cancel each other. Carbon dioxide therefore has a dipole moment of 0 D.

Another symmetrical molecule is carbon tetrachloride (CCl_4). The four atoms bonded to the sp^3 carbon atom are identical and project symmetrically out from the carbon atom. Thus, as with CO_2, the symmetry of the molecule causes the bond dipole moments to cancel. Therefore, carbon tetrachloride also has no dipole moment.

The dipole moment of chloromethane (CH_3Cl) is greater (1.87 D) than the dipole moment of its C—Cl bond (1.5 D) because the C—H dipoles are oriented so that they reinforce the dipole of the C—Cl bond. In other words, all the electrons are pulled in the same general direction.

The dipole moment of water (1.85 D) is greater than the dipole moment of a single O—H bond (1.5 D) because the dipoles of the two O—H bonds reinforce each other; the lone-pair electrons also contribute to the dipole moment. Similarly, the dipole moment of ammonia (1.47 D) is greater than the dipole moment of a single N—H bond (1.3 D).

PROBLEM 35

Account for the difference in the shape and color of the potential maps for ammonia and the ammonium ion in Section 1.11.

PROBLEM 36♦

Which of the following molecules would you expect to have a dipole moment of zero?

a. CH_3CH_3 **b.** $H_2C{=}O$ **c.** CH_2Cl_2 **d.** $H_2C{=}CH_2$ **e.** $H_2C{=}CHBr$

SOME IMPORTANT THINGS TO REMEMBER

- **Organic compounds** are compounds that contain carbon.
- The **atomic number** of an atom is the number of protons in its nucleus (or the number of electrons that surround the neutral atom).
- The **mass number** of an atom is the sum of its protons and neutrons.
- **Isotopes** have the same atomic number, but different mass numbers.
- **Atomic weight** is the average mass of the atoms in the element.
- **Molecular weight** is the sum of the atomic weights of all the atoms in the molecule.
- An **atomic orbital** tells us the volume of space around the nucleus where an electron is most likely to be found.
- The closer the atomic orbital is to the nucleus, the lower is its energy.
- **Minimum energy** corresponds to **maximum stability.**
- Electrons are assigned to orbitals according to three rules: an electron goes into the available orbital with the lowest energy; no more than two electrons can be in an orbital; and an electron will occupy an empty orbital before pairing up with an electron in an orbital with the same energy.
- An atom is most stable if its outer shell is either filled or contains eight electrons, and if it has no electrons of higher energy.
- The **octet rule** states that an atom will give up, accept, or share electrons in order to fill its outer shell or attain an outer shell with eight electrons.
- Electronegativity is a measure of the ability of an atom to pull its bonding electrons toward itself.
- The **electronic configuration** of an atom describes the atomic orbitals occupied by the atom's electrons.
- A **proton** is a positively charged hydrogen ion; a **hydride ion** is a negatively charged hydrogen ion.
- An **ionic bond** results from the attraction between ions with opposite charges.
- A **covalent bond** is formed when two atoms share a pair of electrons.
- A **polar covalent bond** is a covalent bond between atoms with different **electronegativities**.
- The greater the difference in electronegativity between the atoms forming the bond, the closer the bond is to the ionic end of the continuum.
- A polar covalent bond has a **dipole** (a positive end and a negative end), measured by a **dipole moment.**
- The **dipole moment** of a molecule depends on the magnitude and direction of all the bond dipole moments.
- **Core electrons** are electrons in inner shells. **Valence electrons** are electrons in the outermost shell. **Lone-pair electrons** are valence electrons that do not form bonds.
- **formal charge** = # of valence electrons – # of electrons the atom has to itself (all of the lone-pair electrons and one-half of the bonding electrons)
- **Lewis structures** indicate which atoms are bonded together and show **lone pairs** and **formal charges.**
- When the atom is neutral, C forms 4 bonds, N forms 3 bonds, O forms 2 bonds, and H or a halogen forms 1 bond.
- When the atom is neutral, N has 1 lone pair, O has 2 lone pairs, and a halogen has 3 lone pairs.

- A **carbocation** has a positively charged carbon, a **carbanion** has a negatively charged carbon, and a **radical** has an unpaired electron.
- All **single bonds** in organic compounds are **sigma** (σ) bonds; side-to-side overlap of parallel *p* orbitals forms a **pi (π) bond.**
- Bond strength is measured by the **bond dissociation energy;** a σ bond is stronger than a π bond.
- To be able to form four bonds, carbon has to promote an electron from an *s* orbital to an empty *p* orbital.
- C, N, O, and the halogens form bonds using **hybrid orbitals.**
- The **hybridization** of C, N, or O depends on the number of π bonds the atom forms: no π bonds = sp^3, one π bond = sp^2, and two π bonds = sp. Exceptions are carbocations and carbon radicals, which are sp^2.
- A **double bond** consists of one σ bond and one π bond; a **triple bond** consists of one σ bond and two π bonds.
- The greater the electron density in the region of orbital overlap, the stronger and shorter the bond.
- Triple bonds are shorter and stronger than double bonds, which are shorter and stronger than single bonds. The shorter the bond, the stronger it is.
- Bonding pairs and lone-pair electrons around an atom stay as far apart as possible.

GLOSSARY

The definitions of the key words used in each chapter can be found at the beginning of each pertinent chapter in the *Study Guide/Solutions Manual.* The definitions of all the key words used in this book can be found in the Glossary on page G-1.

PROBLEMS

37. Draw a Lewis structure for each of the following species:
a. H_2CO_3 **b.** CO_3^{2-} **c.** CH_2O **d.** CO_2

38. a. Which of the following has a nonpolar covalent bond?
b. Which of the following has a bond closest to the ionic end of the bond spectrum?
CH_3NH_2 CH_3CH_3 CH_3F CH_3OH

39. What is the hybridization of all the atoms (other than hydrogen) in each of the following species? What are the bond angles around each atom?
a. NH_3 **b.** $^{-}CH_3$ **c.** $^{+}NH_4$ **d.** $^{+}CH_3$ **e.** HCN **f.** $C(CH_3)_4$ **g.** H_3O^+

40. Give each atom the appropriate formal charge:
a. $H\!:\!\ddot{\underset{\cdot\cdot}{O}}\!:$ **b.** $H\!:\!\ddot{\underset{\cdot\cdot}{O}}\cdot$ **c.** $H-\ddot{\underset{\cdot\cdot}{N}}-H$ **d.** $H-\ddot{C}-H$

41. Draw the condensed structure of a compound that contains only carbon and hydrogen atoms and that has
a. three sp^3 hybridized carbons.
b. one sp^3 hybridized carbon and two sp^2 hybridized carbons.
c. two sp^3 hybridized carbons and two *sp* hybridized carbons.

42. Predict the approximate bond angles:
a. the H—N—H bond angle in NH_3
b. the C—O—C bond angle in CH_3OCH_3
c. the N—C—C bond angle in H_2NCH_2COOH
d. the C—O—H bond angle in CH_3COOH

43. Write the electronic configuration for the following species (carbon's electronic configuration is written as $1s^22s^22p^2$):
a. Na **b.** Na^+ **c.** Ne **d.** Ne^{2-}

44. Draw a Lewis structure for each of the following species:
a. CH_3NH_2 **b.** HNO_2 **c.** N_2H_4 **d.** NH_2O^-

45. Only one of the following formulas describes a compound that exists. Fix the other formulas so they also describe compounds that exist.

a. CH_3 **c.** CH_3OH_2 **e.** $(CH_3)_3C$

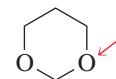
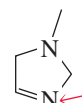
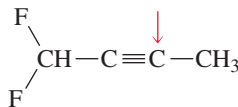
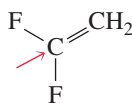
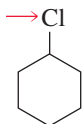
b. CH_4COOH **d.** $CHCl_3OH$ **f.** CCl_4

46. List the bonds in order from most polar to least polar.

a. C—C, C—Si, C—Ge **b.** Si—H, C—H, H—H **c.** H—F, H—I, H—Br **d.** C—H, C—Br, C—N

47. What is the hybridization of the indicated atom in each of the following molecules?

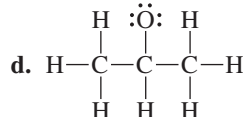
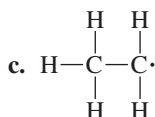
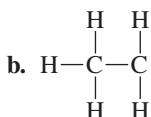
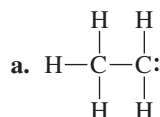
a. sp^3 **b.** sp^2 **c.** sp **d.** sp^2 **e.** sp^3

F₂C=CH₂ ; F₂CH—C≡C—CH₃

48. Write the Kekulé structure for each of the following compounds:

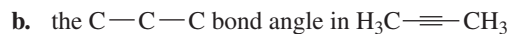
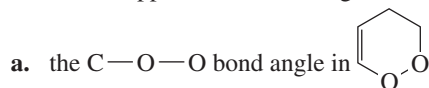
a. CH_3CHO **c.** CH_3COOH **e.** $CH_3CH(OH)CH_2CN$

b. CH_3OCH_3 **d.** $(CH_3)_3COH$ **f.** $(CH_3)_2CHCH(CH_3)CH_2C(CH_3)_3$

49. Assign the missing formal charges.

a. H—C(H)(H)—C(H)(H): **b.** H—C(H)(H)—C(H)(H) **c.** H—C(H)(H)—C(H)(H)· **d.** H—C(H)(H)—C(:Ö:)(H)—C(H)(H)—H

50. Predict the approximate bond angles for the following:

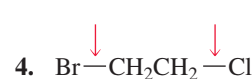
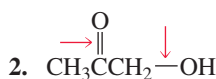
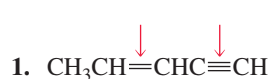
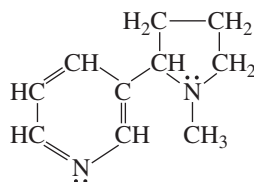
a. the C—O—O bond angle in [ring structure with O—O]

b. the C—C—C bond angle in $H_3C—C≡C—CH_3$

51. Show the direction of the dipole moment in each of the following bonds (use the electronegativities given in Table 1.3):

a. $H_3C—Br$ **b.** $H_3C—Li$ **c.** $HO—NH_2$ **d.** I—Br **e.** $H_3C—OH$ **f.** $(CH_3)_2N—H$

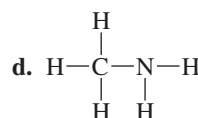
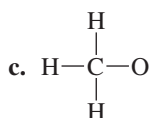
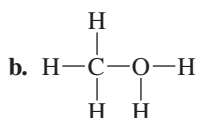
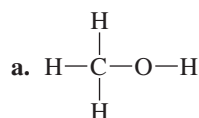
52. a. Which of the indicated bonds in each compound is shorter?

b. Indicate the hybridization of the C, O, N, and halogen atoms in each of the compounds.

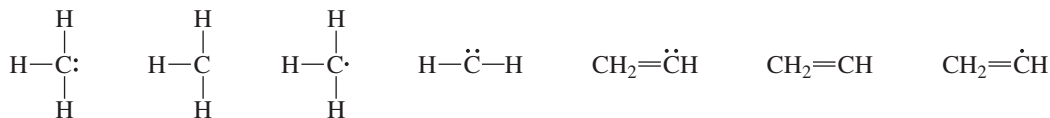
1. $CH_3CH{=}CHC{\equiv}CH$ **2.** $CH_3C(=O)CH_2—OH$ **3.** $CH_3NH—CH_2CH_2N{=}CHCH_3$ **4.** $Br—CH_2CH_2—Cl$

53. In which orbitals are the lone pairs in nicotine?

nicotine

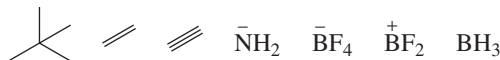
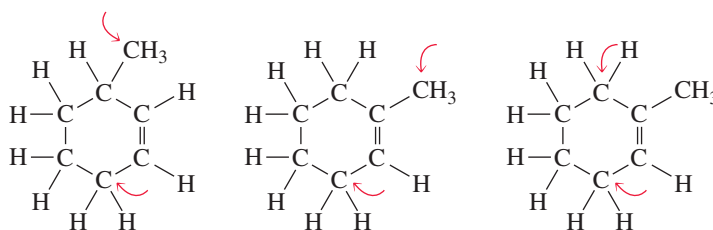
nicotine increases the concentration of dopamine in the brain; the release of dopamine makes a person feel good—the reason why nicotine is addictive

54. Draw the missing lone-pair electrons and assign the missing formal charges for the following:

a. H—C(H)(H)—O—H **b.** H—C(H)(H)—O(H)—H **c.** H—C(H)(H)—O **d.** H—C(H)(H)—N(H)—H

55. Rank the following compounds from highest dipole moment to lowest dipole moment:

56. Indicate the formal charge on each carbon that has one. All lone pairs are shown.

$H_3C\!:$ $\quad$ CH_3 (H—C with three H) $\quad$ $H_3C\cdot$ $\quad$ H—C̈—H $\quad$ $CH_2{=}\ddot{C}H$ $\quad$ $CH_2{=}CH$ $\quad$ $CH_2{=}\dot{C}H$

57. a. Which of the species have bond angles of 109.5°? **b.** Which of the species have bond angles of 120°?

$\bar{N}H_2$ $\quad$ $\bar{B}F_4$ $\quad$ $\overset{+}{B}F_2$ $\quad$ BH_3

58. Do the sp^2 carbons and the indicated sp^3 carbons lie in the same plane?

59. Sodium methoxide (CH_3ONa) has both ionic and covalent bonds. Which bond is ionic? How many covalent bonds does it have?

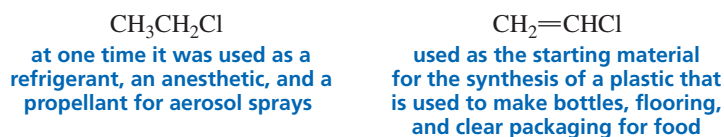
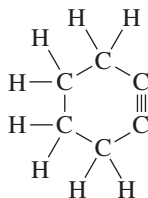
60. a. Why is a H—H bond (0.74 Å) shorter than a C—C bond (1.54 Å)?

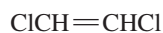
b. Predict the length of a C—H bond.

61. Which compound has a larger dipole moment, $CHCl_3$ or CH_2Cl_2?

62. Which compound has a longer C—Cl bond?

CH_3CH_2Cl — at one time it was used as a refrigerant, an anesthetic, and a propellant for aerosol sprays

$CH_2{=}CHCl$ — used as the starting material for the synthesis of a plastic that is used to make bottles, flooring, and clear packaging for food

63. Explain why the following compound is not stable:

64. The following compound has two isomers. One isomer has a dipole moment of 0 D, whereas the other has a dipole moment of 2.95 D. Propose structures for the two isomers that are consistent with these data.

$$ClCH{=}CHCl$$

2 Acids and Bases: Central to Understanding Organic Chemistry

Decades of acid rain have devastated the Norway Spruce trees near Hora Svatého Šebestiána in the Czech Republic.

The chemistry you will learn in this chapter explains such things as the cause of acid rain and why it destroys monuments and plants, why exercise increases the rate of breathing, how Fosamax prevents bones from being nibbled away, why blood has to be buffered, and how that buffering is accomplished. Acids and bases play an important role in organic chemistry. What you learn about them in this chapter will reappear in almost every other chapter in the book in one form or another. The importance of organic acids and bases will become particularly clear when you learn how and why organic compounds react.

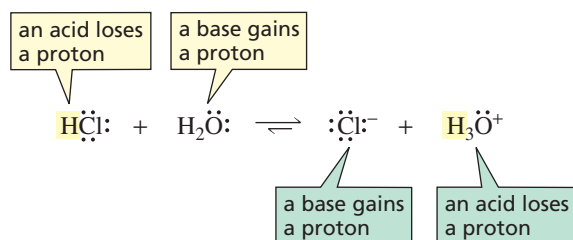
It is hard to believe now, but at one time chemists characterized compounds by tasting them. Early chemists called any compound that tasted sour an acid (from *acidus*, Latin for "sour"). Some familiar acids are citric acid (found in lemons and other citrus fruits), acetic acid (found in vinegar), and hydrochloric acid (found in stomach acid—the sour taste associated with vomiting).

Compounds that neutralize acids, thereby destroying their acidic properties, were called bases, or alkaline compounds. Glass cleaners and solutions designed to unclog drains are familiar alkaline solutions.

2.1 AN INTRODUCTION TO ACIDS AND BASES

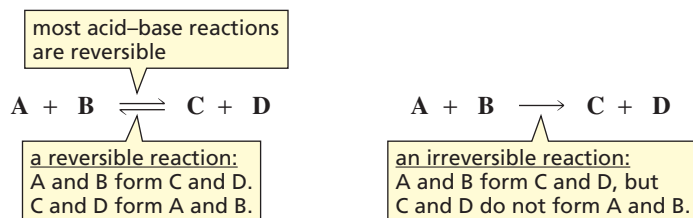
We will look at two definitions for the terms *acid* and *base,* the Brønsted–Lowry definitions and the Lewis definitions.

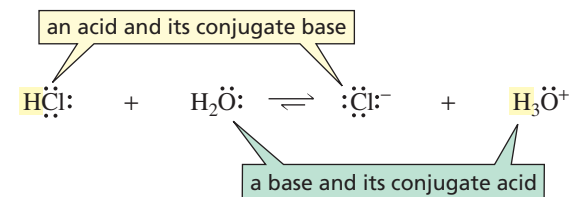
According to Brønsted and Lowry, an **acid** is a species that loses a proton, and a **base** is a species that gains a proton. (Remember that positively charged hydrogen ions are called protons.) For example, in the reaction shown next, hydrogen chloride (HCl) is an acid because it loses a proton, and water is a base because it gains a proton.

In the reverse reaction, H_3O^+ is an acid because it loses a proton, and Cl^- is a base because it gains a proton.

Water can accept a proton because it has two lone pairs, either of which can form a covalent bond with the proton, and Cl^- can accept a proton because any one of its lone pairs can form a covalent bond with a proton. Thus, according to the Brønsted–Lowry definitions:

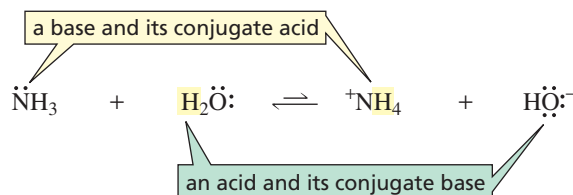
Any species that has a hydrogen can potentially act as an acid.

Any species that has a lone pair can potentially act as a base.

The reaction of an acid with a base is called an **acid–base reaction** or a **proton transfer reaction.** Both an acid and a base must be present in an acid–base reaction, because an acid cannot lose a proton unless a base is present to accept it. Most *acid–base reactions are* ***reversible.*** Two half-headed arrows are used to designate reversible reactions. In Section 2.5, we will see how we can determine whether reactants or products are favored when the reaction has reached equilibrium.

Most acid–base reactions are reversible.

When an acid loses a proton, the resulting species without the proton is called the **conjugate base** of the acid. Thus, Cl^- is the conjugate base of HCl, and H_2O is the conjugate base of H_3O^+. When a base gains a proton, the resulting species with the proton is called the **conjugate acid** of the base. Thus, HCl is the conjugate acid of Cl^-, and H_3O^+ is the conjugate acid of H_2O.

A conjugate base is formed by removing a proton from an acid.

A conjugate acid is formed by adding a proton to a base.

Another example of an acid–base reaction is the reaction between ammonia and water: ammonia (NH_3) is a base because it gains a proton, and water is an acid because it loses a proton. In the reverse reaction, ammonium ion ($^+NH_4$) is an acid because it loses a proton, and hydroxide ion (HO^-) is a base because it gains a proton. Thus, HO^- is the conjugate base of H_2O, $^+NH_4$ is the conjugate acid of NH_3, NH_3 is the conjugate base of $^+NH_4$, and H_2O is the conjugate acid of HO^-.

Notice that in the first of these two reactions water is a base, and in the second it is an acid. Water can behave as a base because it has a lone pair, and it can behave as an acid because it has a proton that it can lose. In Section 2.4, we will see how we can predict that water is a base in the first reaction and is an acid in the second reaction.

A strong base has a high affinity for a proton.

A weak base has a low affinity for a proton.

Acidity is a measure of the tendency of a compound to lose a proton, whereas **basicity** is a measure of a compound's affinity for a proton. A strong acid is one that has a strong tendency to lose a proton. This means that its conjugate base must be weak because it has little affinity for the proton. A weak acid has little tendency to lose its proton, indicating that its conjugate base is strong because it has a high affinity for the proton. Thus, the following important relationship exists between an acid and its conjugate base:

The stronger the acid, the weaker its conjugate base.

For example, HBr is a stronger acid than HCl, so Br^- is a weaker base than Cl^-.

PROBLEM 1♦

Which of the following are *not* acids?

CH_3COOH CO_2 HNO_2 $HCOOH$ CCl_4

PROBLEM 2♦

Draw the products of the acid–base reaction when

a. HCl is the acid and NH_3 is the base. **b.** H_2O is the acid and $^-NH_2$ is the base.

PROBLEM 3♦

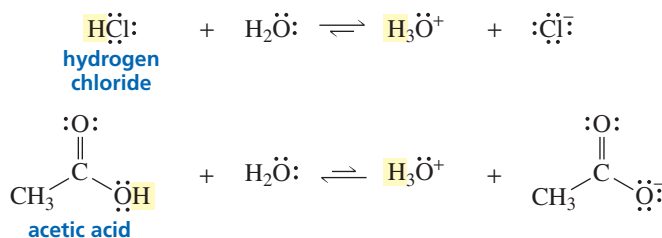
a. What is the conjugate acid of each of the following?
 1. NH_3 **2.** Cl^- **3.** HO^- **4.** H_2O

b. What is the conjugate base of each of the following?
 1. NH_3 **2.** HBr **3.** HNO_3 **4.** H_2O

2.2 pK_a AND pH

When a strong acid such as hydrogen chloride is dissolved in water, almost all the molecules dissociate (break into ions), which means that the *products* are favored at equilibrium—the equilibrium lies to the right. When a much weaker acid, such as acetic acid, is dissolved in water, very few molecules dissociate, so the *reactants* are favored at equilibrium—the equilibrium lies to the left. A longer arrow is drawn toward the species favored at equilibrium.

$$\underset{\text{hydrogen chloride}}{HCl} + H_2O \rightleftharpoons H_3O^+ + Cl^-$$

$$\underset{\text{acetic acid}}{CH_3COOH} + H_2O \rightleftharpoons H_3O^+ + CH_3COO^-$$

The degree to which an acid (HA) dissociates in an aqueous solution is indicated by the **acid dissociation constant,** K_a. Brackets are used to indicate the concentrations of the reactants and products (in moles/liter).

$$HA \rightleftharpoons H_3O^+ + A^-$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

The larger the acid dissociation constant, the stronger is the acid—that is, the greater is its tendency to lose a proton. Hydrogen chloride, with an acid dissociation constant of 10^7, is a stronger acid than acetic acid, with an acid dissociation constant of 1.74×10^{-5}. For convenience, the strength of an acid is generally indicated by its **pK_a** value rather than its K_a value, where

The stronger the acid, the more readily it loses a proton.

$$pK_a = -\log K_a$$

The pK_a of hydrogen chloride is -7 and the pK_a of acetic acid, a much weaker acid, is 4.76. Notice that the stronger the acid, the smaller its pK_a value.

The stronger the acid, the smaller its pK_a value.

very strong acids	$pK_a < 1$
moderately strong acids	$pK_a = 1-3$
weak acids	$pK_a = 3-5$
very weak acids	$pK_a = 5-15$
extremely weak acids	$pK_a > 15$

The concentration of protons in a solution is indicated by **pH**. This concentration can be written as either $[H^+]$ or, because a proton in water is solvated, as $[H_3O^+]$.

$$pH = -\log [H^+]$$

The pH values of some commonly encountered solutions are shown in the margin; the lower the pH, the more acidic the solution. Thus, we see that lemon juice is more acidic than coffee, and rain is more acidic than milk. Solutions with pH values less than 7 are acidic, whereas those with pH values greater than 7 are basic. The pH of a solution can be changed simply by adding acid or base to the solution.

Do not confuse pH and pK_a. The pH scale is used to describe the acidity of a *solution*, whereas the pK_a indicates the tendency of a compound to lose its proton. Thus, the pK_a is characteristic of a particular compound, much like a melting point or a boiling point.

PROBLEM 4♦

a. Which is a stronger acid, one with a pK_a of 5.2 or one with a pK_a of 5.8?
b. Which is a stronger acid, one with an acid dissociation constant of 3.4×10^{-3} or one with an acid dissociation constant of 2.1×10^{-4}?

PROBLEM 5♦

Butyric acid, the compound responsible for the unpleasant odor and taste of sour milk, has a pK_a value of 4.82. Vitamin C has a pK_a value of 4.17. Is butyric acid a stronger acid or a weaker acid than vitamin C?

PROBLEM 6

Antacids are compounds that neutralize stomach acid. Write the equations that show how Milk of Magnesia, Alka-Seltzer, and Tums remove excess acid.

a. Milk of Magnesia: $Mg(OH)_2$
b. Alka-Seltzer: $KHCO_3$ and $NaHCO_3$
c. Tums: $CaCO_3$

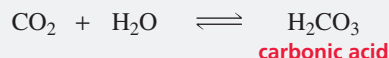
PROBLEM 7♦

Are the following body fluids acidic or basic?

a. bile (pH = 8.4) **b.** urine (pH = 5.9) **c.** spinal fluid (pH = 7.4)

Acid Rain

Rain is mildly acidic (pH = 5.5) because water reacts with the CO_2 in the air to form carbonic acid (a weak acid with a pK_a value of 6.4).

$$CO_2 + H_2O \rightleftharpoons \underset{\text{carbonic acid}}{H_2CO_3}$$

In some parts of the world, rain has been found to be much more acidic (pH values as low as 4.3). This so-called acid rain is formed where sulfur dioxide and nitrogen oxides are produced, because water reacts with these gases to form strong acids—sulfuric acid (pK_a = −5.0) and nitric acid (pK_a = −1.3). Burning fossil fuels for the generation of electric power is the factor most responsible for forming these acid-producing gases.

Acid rain has many deleterious effects. It can destroy aquatic life in lakes and streams; it can make soil so acidic that crops cannot grow and forests can be destroyed (see page 68); and it can cause the deterioration of paint and building materials, including monuments and statues that are part of our cultural heritage. Marble—a form of calcium carbonate—decays because protons react with CO_3^{2-} to form carbonic acid, which decomposes to CO_2 and H_2O (the reverse of the reaction shown above on the left).

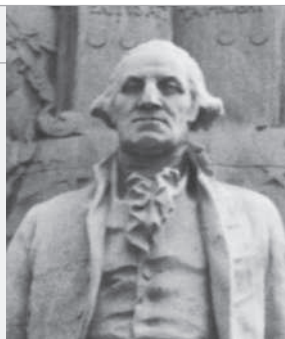
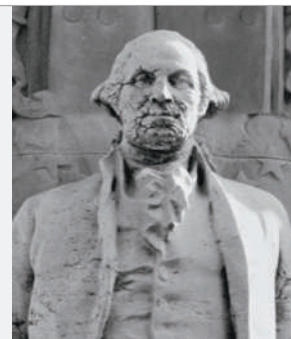
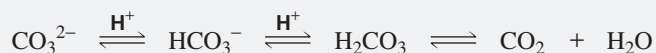



photo taken in 1935

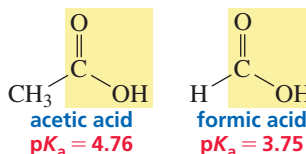
photo taken in 1994

Statue of George Washington in Washington Square Park, in Greenwich Village, New York.

$$CO_3^{2-} \overset{H^+}{\rightleftharpoons} HCO_3^- \overset{H^+}{\rightleftharpoons} H_2CO_3 \rightleftharpoons CO_2 + H_2O$$

2.3 ORGANIC ACIDS AND BASES

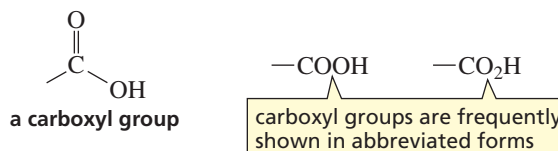
The most common organic acids are carboxylic acids—compounds that have a COOH group. Acetic acid and formic acid are examples of carboxylic acids. Carboxylic acids have pK_a values ranging from about 3 to 5, so they are weak acids. The pK_a values of a wide variety of organic compounds are listed in Appendix I.

CH_3COOH — acetic acid, pK_a = 4.76

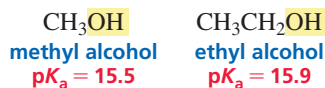
$HCOOH$ — formic acid, pK_a = 3.75

The carboxyl group of a carboxylic acid can be represented in different ways.

a carboxyl group

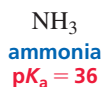
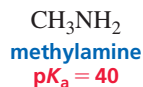
—COOH —CO_2H

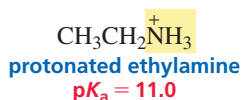
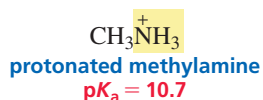
carboxyl groups are frequently shown in abbreviated forms

Alcohols—compounds that have an OH group—are much weaker acids than carboxylic acids, with pK_a values close to 16. Methyl alcohol and ethyl alcohol are examples of alcohols. We will see why carboxylic acids are stronger acids than alcohols in Section 2.8.

CH_3OH — methyl alcohol, pK_a = 15.5

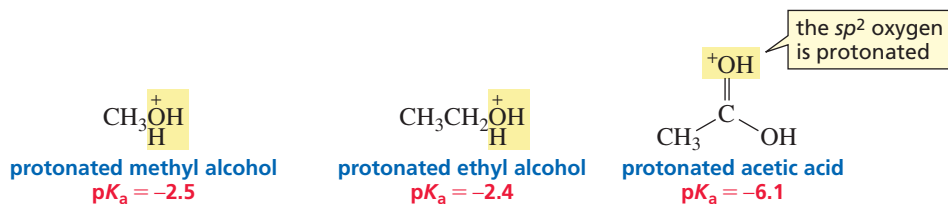
CH_3CH_2OH — ethyl alcohol, pK_a = 15.9

Amines are compounds that result from replacing one or more of the hydrogens bonded to ammonia with a carbon-containing subsitutent. Amines and ammonia have such high

pK_a values that they rarely behave as acids—they are much more likely to act as bases. In fact, they are the most common organic bases. We will see why alcohols are stronger acids than amines in Section 2.6.

CH_3NH_2	NH_3
methylamine	**ammonia**
$pK_a = 40$	**$pK_a = 36$**

We can assess the strength of a base by considering the strength of its conjugate acid—remembering that *the stronger the acid, the weaker its conjugate base*. For example, based on their pK_a values, protonated methylamine (10.7) is a stronger acid than protonated ethylamine (11.0), which means that methylamine is a weaker base than ethylamine. (A protonated compound is a compound that has gained an additional proton.) Notice that the pK_a values of protonated amines are about 11.

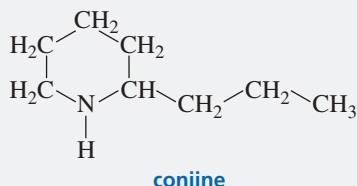
$CH_3\overset{+}{N}H_3$	$CH_3CH_2\overset{+}{N}H_3$
protonated methylamine	**protonated ethylamine**
$pK_a = 10.7$	**$pK_a = 11.0$**

Protonated alcohols and protonated carboxylic acids are very strong acids. For example, protonated methyl alcohol has a pK_a of −2.5, protonated ethyl alcohol has a pK_a of −2.4, and protonated acetic acid has a pK_a of −6.1.

$CH_3\overset{+}{O}H$ (H)	$CH_3CH_2\overset{+}{O}H$ (H)	$CH_3C(=\overset{+}{O}H)OH$
protonated methyl alcohol	**protonated ethyl alcohol**	**protonated acetic acid**
$pK_a = -2.5$	**$pK_a = -2.4$**	**$pK_a = -6.1$**

the sp^2 oxygen is protonated

Notice that it is the sp^2 oxygen of the carboxylic acid that is protonated (meaning that it acquires the proton). We will see why this is so in Section 11.9.

Poisonous Amines

Exposure to poisonous plants is responsible for an average of 63,000 calls each year to poison control centers. Hemlock is an example of a plant known for its toxicity. It contains eight different poisonous amines—the most abundant primary one is coniine, a neurotoxin that disrupts the central nervous system. Ingesting even a small amount can be fatal because it causes respiratory paralysis, which results in oxygen deprivation to the brain and heart. A poisoned person can recover if artificial respiration is applied until the drug can be flushed from the system. A drink made of hemlock was used to put Socrates to death in 399 BC; he was condemned for failing to acknowledge the gods that natives of the city of Athens worshipped.

coniine

hemlock

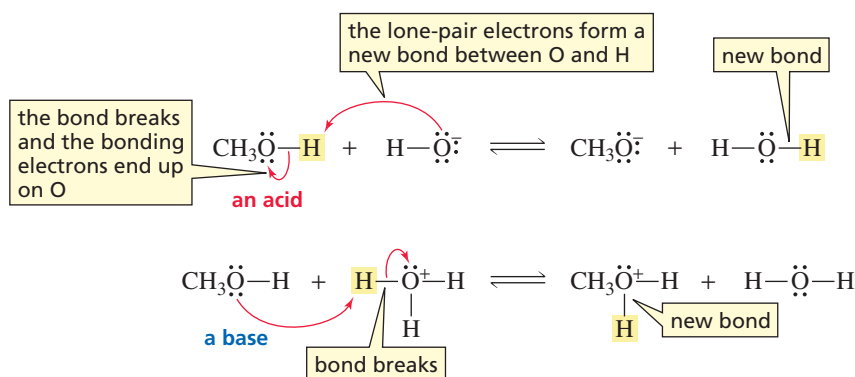
We saw in Section 2.1 that water can behave both as an acid and as a base. An alcohol, too, can behave as an acid and lose a proton, or it can behave as a base and gain a proton.

A curved arrow points *from* the electron donor *to* the electron acceptor.

$$CH_3\ddot{O}-H + H-\ddot{O}:^- \rightleftharpoons CH_3\ddot{O}:^- + H-\ddot{O}-H$$

the bond breaks and the bonding electrons end up on O; an acid; the lone-pair electrons form a new bond between O and H; new bond

$$CH_3\ddot{O}-H + H-\ddot{O}^+-H \rightleftharpoons CH_3\ddot{O}^+-H + H-\ddot{O}-H$$

a base; bond breaks; new bond

Chemists frequently use curved arrows to indicate the bonds that are broken and formed as reactants are converted into products. They are called *curved arrows* to distinguish them from the *straight* arrows used to link reactants with products in the equation for a chemical reaction. Each curved arrow with a two-barbed arrowhead signifies the movement of two electrons. The arrow always points *from* the electron donor *to* the electron acceptor.

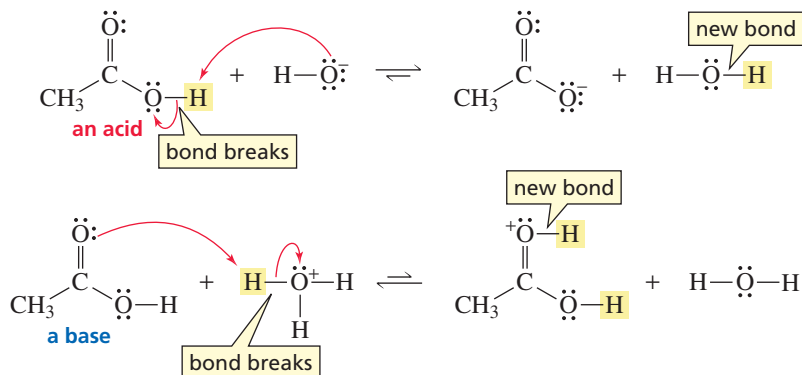
In an acid–base reaction, one of the arrows is drawn *from* a lone pair on the base *to* the proton of the acid. A second arrow is drawn *from* the electrons that the proton shared *to* the atom on which they are left behind. As a result, the curved arrows let you follow the electrons to see what bond is broken and what bond is formed in the reaction.

A carboxylic acid also can behave as an acid (lose a proton) or as a base (gain a proton).

$$CH_3C(=\ddot{O})\ddot{O}-H + H-\ddot{O}:^- \rightleftharpoons CH_3C(=\ddot{O})\ddot{O}:^- + H-\ddot{O}-H$$

an acid; bond breaks; new bond

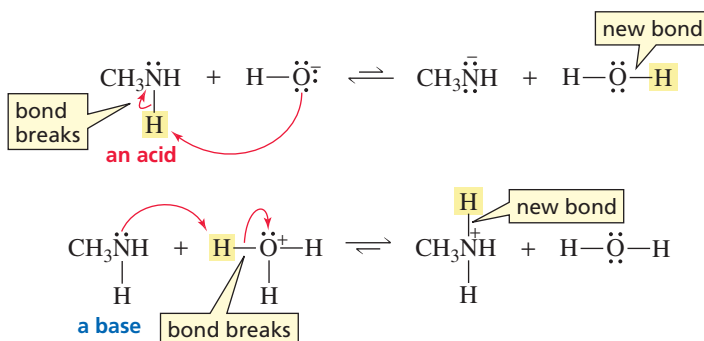
$$CH_3C(=\ddot{O})\ddot{O}-H + H-\ddot{O}^+-H \rightleftharpoons CH_3C(=\ddot{O}^+-H)\ddot{O}-H + H-\ddot{O}-H$$

a base; bond breaks; new bond

Similarily, an amine can behave as an acid (lose a proton) or as a base (gain a proton).

$$CH_3\ddot{N}H-H + H-\ddot{O}:^- \rightleftharpoons CH_3\ddot{N}^-H + H-\ddot{O}-H$$

bond breaks; an acid; new bond

$$CH_3\ddot{N}H_2 + H-\ddot{O}^+H-H \rightleftharpoons CH_3\overset{+}{N}H_3 + H-\ddot{O}-H$$

a base; bond breaks; new bond

It is important to know the approximate pK_a values of the various classes of compounds we have looked at so far. An easy way to remember them is in units of five, as shown in Table 2.1. (R is used when the particular carboxylic acid, alcohol, or amine is not specified.) Protonated alcohols, protonated carboxylic acids, and protonated water have pK_a values less than 0, carboxylic acids have pK_a values of ~5, protonated amines

have pK_a values of ~10, and alcohols and water have pK_a values of ~15. These values are also listed inside the back cover of this book for easy reference.

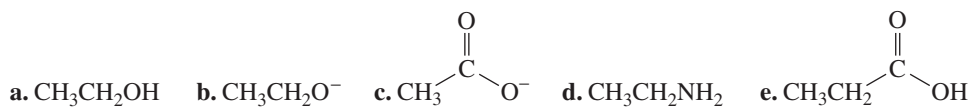
Table 2.1 Approximate pK_a Values

pK_a < 0	pK_a ~ 5	pK_a ~ 10	pK_a ~ 15
$R\overset{+}{O}H_2$ a protonated alcohol	RC(=O)OH a carboxylic acid	$R\overset{+}{N}H_3$ a protonated amine	ROH an alcohol
RC(=$\overset{+}{O}$H)OH a protonated carboxylic acid			H_2O water
H_3O^+ protonated water			

You need to remember these approximate pK_a values because they will be very important when you learn about the reactions of organic compounds.

PROBLEM 8♦

Draw the conjugate acid of each of the following:

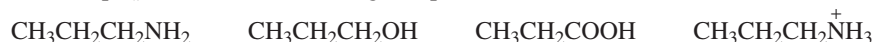
a. CH_3CH_2OH **b.** $CH_3CH_2O^-$ **c.** $CH_3C(=O)O^-$ **d.** $CH_3CH_2NH_2$ **e.** $CH_3CH_2C(=O)OH$

PROBLEM 9

a. Write an equation showing CH_3OH reacting as an acid with NH_3 and an equation showing it reacting as a base with HCl.

b. Write an equation showing NH_3 reacting as an acid with CH_3O^- and an equation showing it reacting as a base with HBr.

PROBLEM 10♦

Estimate the pK_a values of the following compounds:

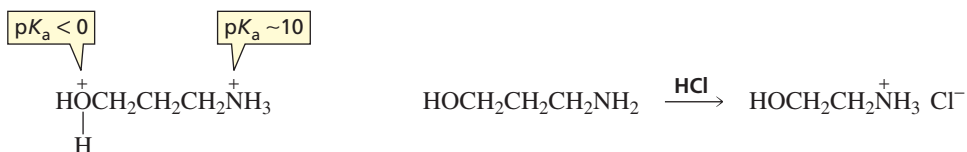
$CH_3CH_2CH_2NH_2$ $CH_3CH_2CH_2OH$ CH_3CH_2COOH $CH_3CH_2CH_2\overset{+}{N}H_3$

PROBLEM-SOLVING STRATEGY

Which atom of the following compound is more apt to be protonated?

$$HOCH_2CH_2CH_2NH_2$$

Solution One way to solve this problem is to look at the pK_a values of the conjugate acids of the groups, remembering that the weaker acid will have the stronger conjugate base. The stronger base will be the one more apt to be protonated.

pK_a < 0 pK_a ~10

$$H\overset{+}{O}(H)CH_2CH_2CH_2\overset{+}{N}H_3 \qquad HOCH_2CH_2CH_2NH_2 \xrightarrow{HCl} HOCH_2CH_2\overset{+}{N}H_3\ Cl^-$$

The conjugate acids have pK_a values of ~0 and ~10. Because the $^+NH_3$ group is the weaker acid, the NH_2 group is the stronger base, so it is the group more apt to be protonated.

Now use the skill you have just learned to solve Problem 11.

PROBLEM 11♦

a. Which is a stronger base, CH_3COO^- or $HCOO^-$? (The pK_a of CH_3COOH is 4.8; the pK_a of HCOOH is 3.8.)

b. Which is a stronger base, HO^- or $^-NH_2$? (The pK_a of H_2O is 15.7; the pK_a of NH_3 is 36.)

c. Which is a stronger base, H_2O or CH_3OH? (The pK_a of H_3O^+ is -1.7; the pK_a of $CH_3\overset{+}{O}H_2$ is -2.5.)

PROBLEM 12♦

Using the pK_a values in Section 2.3, rank the following species in order from strongest base to weakest base:

$$CH_3NH_2 \quad CH_3\overset{-}{N}H \quad CH_3OH \quad CH_3O^- \quad CH_3\overset{\overset{O}{\|}}{C}O^-$$

2.4 HOW TO PREDICT THE OUTCOME OF AN ACID–BASE REACTION

Now let's see how we can predict that water will behave as a base when it reacts with HCl (the first reaction in Section 2.1) but as an acid when it reacts with NH_3 (the second reaction in Section 2.1). To determine which of two reactants will be the acid, we need to compare their pK_a values.

For the reaction of H_2O with HCl: the reactants are water (pK_a = 15.7) and HCl (pK_a = −7). Because HCl is the stronger acid (it has the lower pK_a value), it will be the reactant that loses a proton. Therefore, HCl is the acid and water is the base in this reaction.

For the reaction of H_2O with NH_3: the reactants are water (pK_a = 15.7) and NH_3 (pK_a = 36). Because water is the stronger acid (it has the lower pK_a value), it will be the reactant that loses a proton. Therefore, water is the acid and ammonia is the base in this reaction.

PROBLEM 13♦

Does methanol behave as an acid or a base when it reacts with methylamine?

2.5 HOW TO DETERMINE THE POSITION OF EQUILIBRIUM

To determine the position of equilibrium for an acid–base reaction (that is, to determine whether reactants or products are favored), we need to compare the pK_a value of the acid on the left of the equilibrium arrows with the pK_a value of the acid on the right of the arrows. The equilibrium favors *formation* of the weaker acid (the one with the higher pK_a value). In other words, the equilibrium lies toward the weaker acid.

$$CH_3COOH + NH_3 \rightleftharpoons CH_3COO^- + \overset{+}{N}H_4$$

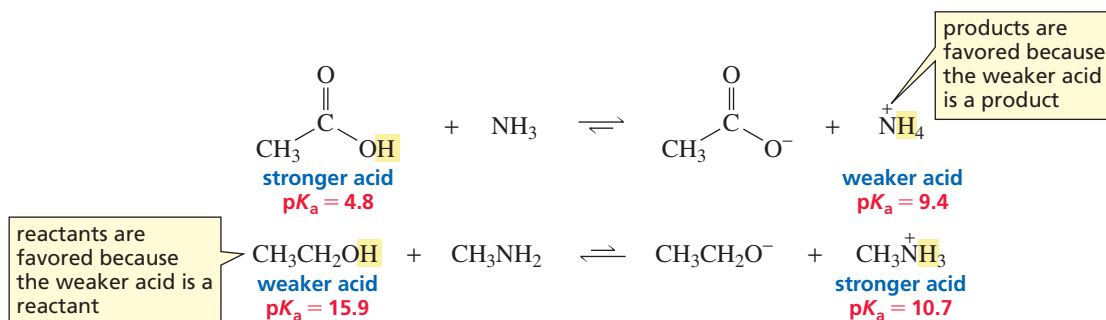
stronger acid pK_a = 4.8 ... weaker acid pK_a = 9.4

products are favored because the weaker acid is a product

$$CH_3CH_2OH + CH_3NH_2 \rightleftharpoons CH_3CH_2O^- + CH_3\overset{+}{N}H_3$$

weaker acid pK_a = 15.9 ... stronger acid pK_a = 10.7

reactants are favored because the weaker acid is a reactant

In an acid–base reaction, the equilibrium favors the formation of the weaker acid.

PROBLEM 14

a. For each of the acid–base reactions in Section 2.3, compare the pK_a values of the acids on either side of the equilibrium arrows to prove that the equilibrium lies in the direction indicated. (The pK_a values you need can be found in Section 2.3 or in Problem 11.)
b. Do the same for the acid–base reactions in Section 2.1.

PROBLEM 15

Ethyne has a pK_a value of 25, water has a pK_a value of 15.7, and ammonia (NH_3) has a pK_a value of 36. Draw the equation, showing equilibrium arrows that indicate whether reactants or products are favored, for the acid–base reaction of ethyne with

a. HO^-. **b.** $^-NH_2$.
c. Which would be a better base to use if you wanted to remove a proton from ethyne, HO^- or $^-NH_2$?

PROBLEM 16♦

Which of the following bases can remove a proton from acetic acid in a reaction that favors products?

HO^- CH_3NH_2 $HC{\equiv}C^-$ CH_3OH H_2O Cl^-

2.6 HOW THE STRUCTURE OF AN ACID AFFECTS ITS pK_a VALUE

The strength of an acid is determined by the stability of the conjugate base that forms when the acid loses its proton: the more stable the base, the stronger its conjugate acid. (The reason for this is explained in Section 5.6.)

Stable bases are weak bases.

A stable base readily bears the electrons it formerly shared with a proton. In other words, stable bases are weak bases—they do not share their electrons well. Thus, we can say either:

The more stable the base, the stronger its conjugate acid.

The weaker the base, the stronger its conjugate acid or
the more stable the base, the stronger its conjugate acid.

The weaker the base, the stronger its conjugate acid.

Electronegativity

Two factors that affect the stability of a base are its *electronegativity* and its *size*.

The atoms in the second row of the periodic table are all *similar in size*, but they have very *different electronegativities*, which increase across the row from left to right. Of the atoms shown, carbon is the least electronegative and fluorine is the most electronegative.

relative electronegativities: C < N < O < F

most electronegative

If we look at the acids formed by attaching hydrogens to these elements, we see that the most acidic compound is the one that has its hydrogen attached to the most electronegative atom. Thus, HF is the strongest acid and methane is the weakest acid.

When the atoms are similar in size,
the strongest acid will have its hydrogen attached to the most electronegative atom.

relative acidities: $CH_4 < NH_3 < H_2O < HF$ (strongest acid)

When atoms are similar in size, the strongest acid has its hydrogen attached to the most electronegative atom.

If we look at the stabilities of the conjugate bases of these acids, we find that they too increase from left to right, because the more electronegative the atom, the better it can bear its negative charge. Thus, *the strongest acid has the most stable (weakest) conjugate base*.

relative stabilities: $^-CH_3 < ^-NH_2 < HO^- < F^-$ (most stable)

The effect that the electronegativity of the atom bonded to a hydrogen has on the compound's acidity can be appreciated when the pK_a values of alcohols and amines are compared. Because oxygen is more electronegative than nitrogen, an alcohol is more acidic than an amine.

CH_3OH **methyl alcohol** pK_a = 15.5

CH_3NH_2 **methylamine** pK_a = 40

Again, because oxygen is more electronegative than nitrogen, a protonated alcohol is more acidic than a protonated amine.

$CH_3\overset{+}{O}H_2$ **protonated methyl alcohol** pK_a = –2.5

$CH_3\overset{+}{N}H_3$ **protonated methylamine** pK_a = 10.7

PROBLEM 17♦

List the ions ($^-CH_3$, $^-NH_2$, HO^-, and F^-) in order from most basic to least basic.

Hybridization

The hybridization of an atom affects the acidity of a hydrogen bonded to it because hybridization affects electronegativity: an *sp* hybridized atom is more electronegative than the same atom that is sp^2 hybridized, which is more electronegative than the same atom that is sp^3 hybridized.

An *sp* carbon is more electronegative than an sp^2 carbon, which is more electronegative than an sp^3 carbon.

relative electronegativities

most electronegative $sp > sp^2 > sp^3$ least electronegative

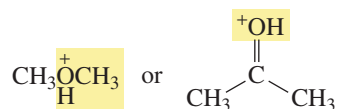
Because the electronegativity of carbon atoms follows the order $sp > sp^2 > sp^3$, ethyne is a stronger acid than ethene, and ethene is a stronger acid than ethane. Again, the most acidic compound is the one with its hydrogen attached to the most electronegative atom.

PROBLEM 18♦

List the carbanions shown in the margin in order from most basic to least basic.

PROBLEM 19♦

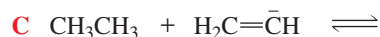
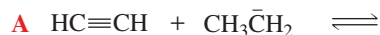
Which is a stronger acid?

$CH_3\overset{+}{O}(H)CH_3$ or $CH_3C(=\overset{+}{O}H)CH_3$

PROBLEM 20

a. Draw the products of the following reactions:

A $HC{\equiv}CH + CH_3\bar{C}H_2 \rightleftharpoons$

B $H_2C{=}CH_2 + HC{\equiv}C^- \rightleftharpoons$

C $CH_3CH_3 + H_2C{=}\bar{C}H \rightleftharpoons$

b. Which of the reactions favor formation of the products?

$HC{\equiv}C^-$

$H_2C{=}\bar{C}H$

$CH_3\bar{C}H_2$

Size

When comparing atoms that are very different in size, the *size* of the atom is more important than its *electronegativity* in determining how well it bears its negative charge. For example, as we proceed down a column in the periodic table, the atoms get larger and the *stability* of the anions *increases* even though the electronegativity of the atoms *decreases*. Because the stability of the bases increases going down the column, the strength of their conjugate acids *increases*. Thus, HI is the strongest acid of the hydrogen halides (that is, I^- is the weakest, most stable base), even though iodine is the least electronegative of the halogens.

When atoms are very different in size,
the strongest acid will have its hydrogen attached to the largest atom.

relative size: $F^- < Cl^- < Br^- < I^-$ (largest)

relative acidities: $HF < HCl < HBr < HI$ (strongest acid)

Size overrides electronegativity when determining relative acidities.

When atoms are very different in size, the strongest acid will have its hydrogen attached to the largest atom.

Why does the size of an atom have such a significant effect on stability that it more than overcomes any difference in electronegativity? The valence electrons of F^- are in a $2sp^3$ orbital, the valence electrons of Cl^- are in a $3sp^3$ orbital, those of Br^- are in a $4sp^3$ orbital, and those of I^- are in a $5sp^3$ orbital. The volume of space occupied by a $3sp^3$ orbital is significantly larger than the volume of space occupied by a $2sp^3$ orbital because a $3sp^3$ orbital extends out farther from the nucleus. Because its negative charge is spread over a larger volume of space, Cl^- is more stable than F^-.

Thus, as a halide ion increases in size (going down the column of the periodic table), its stability increases because its negative charge is spread over a larger volume of space (its electron density decreases). As a result, HI is the strongest acid of the hydrogen

HF

HCl

HBr

HI

halides because I^- is the most stable halide ion (see Table 2.2). The potential maps illustrate the large difference in size of the hydrogen halides.

Table 2.2 The pK_a Values of Some Simple Acids

CH_4 pK_a = 60	NH_3 pK_a = 36	H_2O pK_a = 15.7	HF pK_a = 3.2
		H_2S pK_a = 7.0	HCl pK_a = −7
			HBr pK_a = −9
			HI pK_a = −10

In summary, atomic size does not change much as we move from left to right across a row of the periodic table, so the atoms' orbitals have approximately the same volume. Thus, electronegativity determines the stability of the base and, therefore, the acidity of its conjugate acid. Atomic size increases as we move down a column of the periodic table, so the volume of the orbitals increases and, therefore, their electron density decreases. The electron density of an orbital is more important than electronegativity in determining the stability of a base and, therefore, the acidity of its conjugate acid.

PROBLEM 21♦

List the halide ions (F^-, Cl^-, Br^-, and I^-) in order from strongest base to weakest base.

PROBLEM 22♦

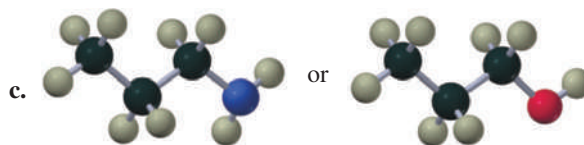
a. Which is more electronegative, oxygen or sulfur?
b. Which is a stronger acid, H_2O or H_2S?
c. Which is a stronger acid, CH_3OH or CH_3SH?

CH_3O^-

CH_3S^-

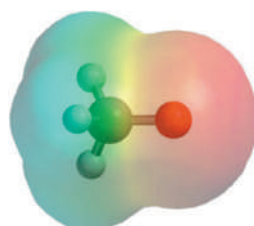
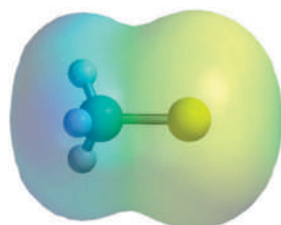
PROBLEM 23♦

Which is a stronger acid?

a. HCl or HBr
b. $CH_3CH_2CH_2\overset{+}{N}H_3$ or $CH_3CH_2CH_2\overset{+}{O}H_2$
c.

black = C, gray = H, blue = N, red = O

d. $CH_3CH_2CH_2OH$ or $CH_3CH_2CH_2SH$

PROBLEM 24♦

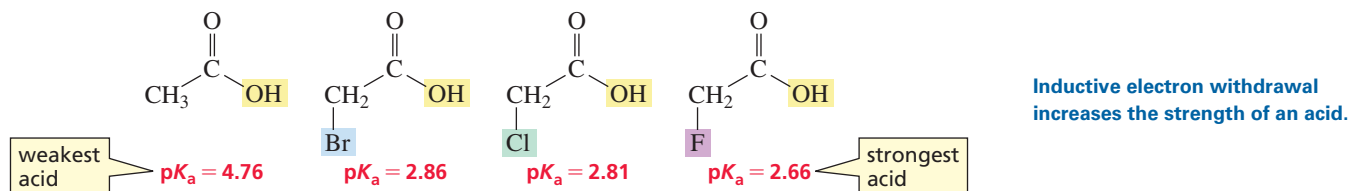
a. Which of the halide ions (F^-, Cl^-, Br^-, and I^-) is the most stable base?
b. Which is the least stable base?
c. Which is the strongest base?

PROBLEM 25♦

Which is a stronger base?

a. H_2O or HO^- **b.** H_2O or NH_3 **c.** $CH_3\overset{O}{\overset{\|}{C}}O^-$ or CH_3O^- **d.** CH_3O^- or CH_3S^-

2.7 HOW SUBSTITUENTS AFFECT THE STRENGTH OF AN ACID

Although the acidic proton of each of the following carboxylic acids is attached to the same atom (an oxygen), the four compounds have different pK_a values:

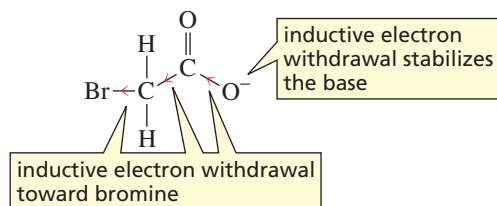
Inductive electron withdrawal increases the strength of an acid.

The different pK_a values indicate that there must be another factor that affects acidity other than the nature of the atom to which the hydrogen is bonded.

From the pK_a values of the four carboxylic acids, we see that replacing one of the hydrogens of the CH_3 group with a halogen increases the acidity of the compound. (The term for replacing an atom in a compound is *substitution*, and the new atom is called a *substituent*.) The halogen is more electronegative than the hydrogen it has replaced, so the halogen pulls the bonding electrons toward itself more than a hydrogen would. Pulling electrons through sigma (σ) bonds is called **inductive electron withdrawal.**

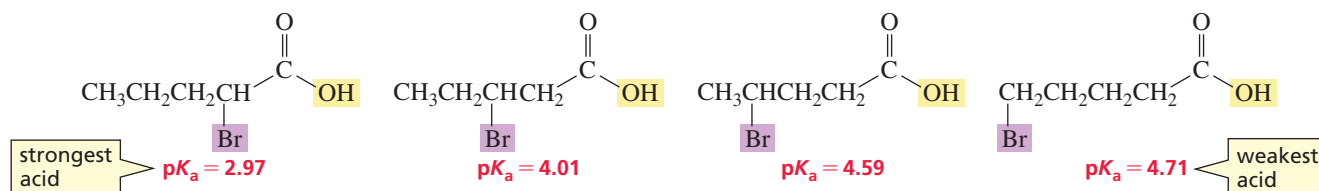
If we look at the conjugate base of a carboxylic acid, we see that inductive electron withdrawal *decreases the electron density* about the oxygen that bears the negative charge, thereby stabilizing it. And we know that stabilizing a base increases the acidity of its conjugate acid.

$Br \leftarrow CH_2 \leftarrow \overset{O}{\overset{\|}{C}} \leftarrow O^-$

inductive electron withdrawal stabilizes the base

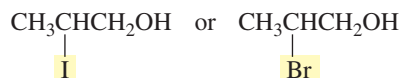
inductive electron withdrawal toward bromine

The pK_a values of the four carboxylic acids shown above decrease (become more acidic) as the electron-withdrawing ability (electronegativity) of the halogen increases. Thus, the fluoro-substituted compound is the strongest acid because its conjugate base is the most stabilized (is the weakest).

The effect a substituent has on the acidity of a compound decreases as the distance between the substituent and the acidic proton increases.

	$CH_3CH_2CH_2CH(Br)COOH$	$CH_3CH_2CH(Br)CH_2COOH$	$CH_3CH(Br)CH_2CH_2COOH$	$CH_2(Br)CH_2CH_2CH_2COOH$	
strongest acid	pK_a = 2.97	pK_a = 4.01	pK_a = 4.59	pK_a = 4.71	weakest acid

PROBLEM-SOLVING STRATEGY

Determining Relative Acid Strength from Structure

Which is a stronger acid?

$$\underset{\displaystyle\text{I}}{CH_3\underset{|}{C}HCH_2OH} \quad \text{or} \quad \underset{\displaystyle\text{Br}}{CH_3\underset{|}{C}HCH_2OH}$$

When you are asked to compare two items, pay attention to where they differ and ignore where they are the same. These two compounds differ only in the halogen that is attached to the middle carbon. Because bromine is more electronegative than iodine, there is greater inductive electron withdrawal from oxygen in the brominated compound. The brominated compound, therefore, will have the more stable conjugate base, so it will be the stronger acid.

Now use the strategy you have just learned to solve Problem 26.

PROBLEM 26♦

Which is a stronger acid?

a. $CH_3OCH_2CH_2OH$ or $CH_3CH_2CH_2CH_2OH$

b. $CH_3CH_2CH_2\overset{+}{N}H_3$ or $CH_3CH_2CH_2\overset{+}{O}H_2$

c. $CH_3OCH_2CH_2CH_2OH$ or $CH_3CH_2OCH_2CH_2OH$

d. $CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2OH$ or $CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}OH$

PROBLEM 27♦

Which is a stronger base?

a. $CH_3\underset{\underset{\displaystyle Br}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}O^-$ or $CH_3\underset{\underset{\displaystyle F}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}O^-$

b. $CH_3\underset{\underset{\displaystyle Cl}{|}}{C}HCH_2\overset{\overset{\displaystyle O}{\|}}{C}O^-$ or $CH_3CH_2\underset{\underset{\displaystyle Cl}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}O^-$

c. $BrCH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}O^-$ or $CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}O^-$

d. $CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2O^-$ or $CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_2O^-$

PROBLEM 28 Solved

If HCl is a weaker acid than HBr, why is $ClCH_2COOH$ a stronger acid than $BrCH_2COOH$?

Solution To compare the acidities of HCl and HBr, we need to compare the stabilities of their conjugate bases, Cl^- and Br^-. (Notice that an H—Cl bond breaks in one compound and an H—Br bond breaks in the other.) Because we know that size is more important than electronegativity in determining stability, we know that Br^- is more stable than Cl^-. Therefore, HBr is a stronger acid than HCl.

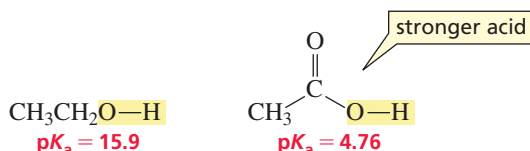
In comparing the acidities of the two carboxylic acids, we again need to compare the stabilities of their conjugate bases, $ClCH_2COO^-$ and $BrCH_2COO^-$. (Notice that an O—H bond breaks in both compounds.) The only way the conjugate bases differ is in the electronegativity of the atom that is drawing electrons away from the negatively charged oxygen. Because Cl is more electronegative than Br, Cl exerts greater inductive electron withdrawal. Thus, it has a greater stabilizing effect on the base that is formed when the proton leaves, so the chloro-substituted compound is the stronger acid.

2.8 AN INTRODUCTION TO DELOCALIZED ELECTRONS

We have seen that a carboxylic acid has a pK_a value of about 5, whereas the pK_a value of an alcohol is about 15. Because a carboxylic acid is a much stronger acid than an alcohol, we know that the conjugate base of a carboxylic acid is considerably more stable than the conjugate base of an alcohol.

$CH_3CH_2O{-}H$ pK_a = 15.9

$CH_3C(=O)O{-}H$ pK_a = 4.76

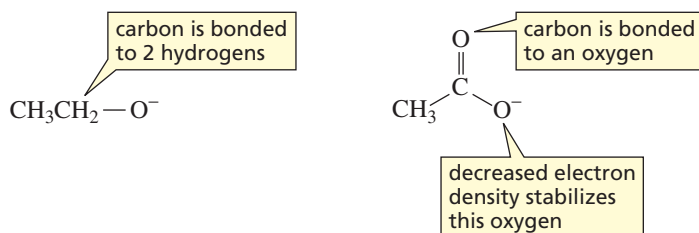
stronger acid

Two factors cause the conjugate base of a carboxylic acid to be more stable than the conjugate base of an alcohol. First, the conjugate base of a carboxylic acid has a doubly bonded oxygen where the conjugate base of an alcohol has two hydrogens. Inductive electron withdrawal by this electronegative oxygen decreases the electron density of the negatively charged oxygen, thereby stabilizing it and increasing the acidity of the conjugate acid.

$CH_3CH_2{-}O^-$

carbon is bonded to 2 hydrogens

$CH_3C(=O)O^-$

carbon is bonded to an oxygen

decreased electron density stabilizes this oxygen

The second factor that causes the conjugate base of the carboxylic acid to be more stable than the conjugate base of the alcohol is *electron delocalization*. When an alcohol loses a proton, the negative charge resides on its single oxygen atom. These electrons are said to be *localized* because they belong to only *one* atom. In contrast, when a carboxylic acid loses a proton, the negative charge is shared by both oxygens. These electrons are *delocalized*.

$CH_3CH_2{-}\ddot{\underset{..}{O}}{:}^-$

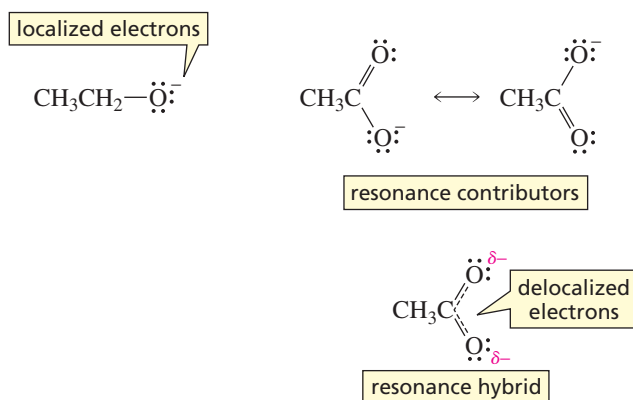
localized electrons

$CH_3C(=\ddot{O}{:}){-}\ddot{O}{:}^- \longleftrightarrow CH_3C(-\ddot{O}{:}^-){=}\ddot{O}{:}$

resonance contributors

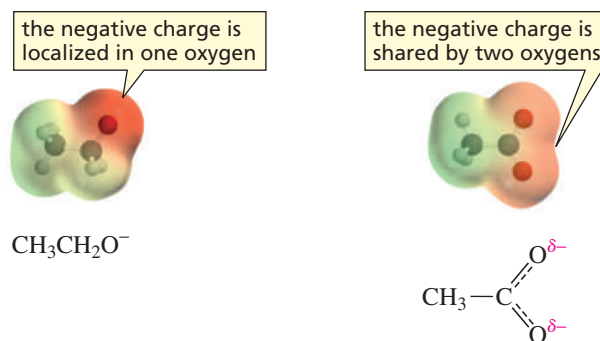
$CH_3C(\cdots O^{\delta-})(\cdots O^{\delta-})$

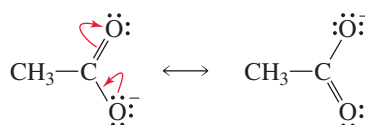
delocalized electrons

resonance hybrid

The two structures shown for the conjugate base of the carboxylic acid are called **resonance contributors.** Neither resonance contributor alone represents the actual structure of the conjugate base. Instead, the actual structure—called a **resonance hybrid**—is a composite of the two resonance contributors. The double-headed arrow between the two resonance contributors is used to indicate that the actual structure is a hybrid.

Delocalized electrons are shared by more than two atoms.

$CH_3CH_2O^-$

$CH_3-C(O^{\delta-})(O^{\delta-})$

Notice that the second resonance contributor is obtained by moving a lone pair toward an sp^2 carbon and breaking the π bond. Thus, two resonance contributors differ only in the location of their π electrons and lone-pair electrons—all the atoms stay in the same place. In the resonance hybrid, an electron pair is spread over *two oxygens and a carbon*.

$$CH_3-C(=\ddot{O}:)-\ddot{O}:^- \longleftrightarrow CH_3-C(-\ddot{O}:^-)=\ddot{O}:$$

The negative charge is shared equally by the two oxygens, and both carbon–oxygen bonds are the same length—they are not as long as a single bond, but they are longer than a double bond. A resonance hybrid can be drawn by using dotted lines to show the delocalized electrons.

Thus, the combination of inductive electron withdrawal and the ability of two atoms to share the negative charge makes the conjugate base of the carboxylic acid more stable than the conjugate base of the alcohol.

Delocalized electrons are very important in organic chemistry—so important that all of Chapter 7 is devoted to them. By that time, you will be thoroughly comfortable with compounds that have only localized electrons, and we can then further explore how to recognize when a compound has delocalized electrons and how delocalized electrons affect the stability, reactivity, and pK_a values of organic compounds.

Fosamax Prevents Bones from Being Nibbled Away

$^-O-P(=O)(OH)-C(OH)(CH_2CH_2CH_2\overset{+}{N}H_3)-P(=O)(OH)-O^-\ Na^+$

Fosamax®

photo of normal bone and bone with osteoporosis

Fosamax is used to treat osteoporosis, a condition characterized by decreased bone density. Under normal conditions, the rate of bone formation and the rate of bone resorption (breakdown) are carefully matched. In osteoporosis, resorption is faster than formation, so bone is nibbled away, causing bones to become fragile (they actually start to resemble honeycombs). Fosamax goes specifically to the sites of bone resorption and inhibits the activity of cells responsible for resorption. Studies have shown that normal bone is then formed on top of Fosamax, and the rate of bone formation becomes faster than the rate of its breakdown. (Trade name labels in this book are green.)

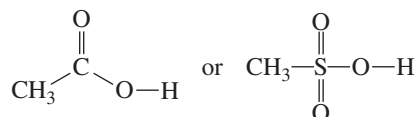
PROBLEM 29

Fosamax has six acidic groups. The structure of the active form of the drug is shown in the box. (Notice that the phosphorus atom in Fosamax and the sulfur atom in Problem 30 can be surrounded by more than eight electrons since P and S are below the second row of the periodic table.)

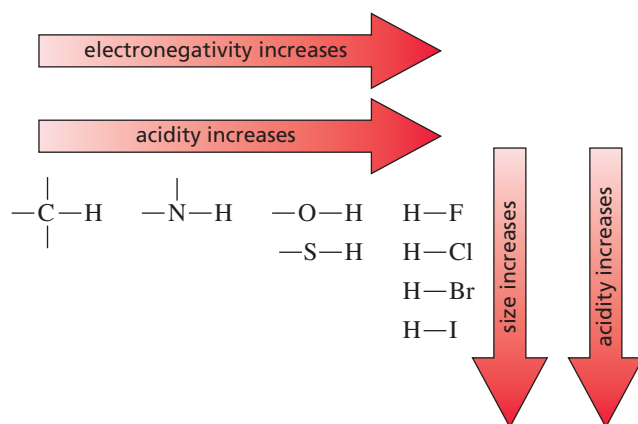
a. The OH groups bonded to phosphorus are the strongest acids of the six groups. Why?
b. Which of the remaining four groups is the weakest acid?

PROBLEM 30♦

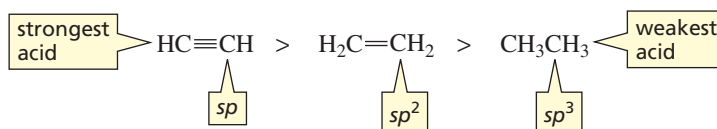
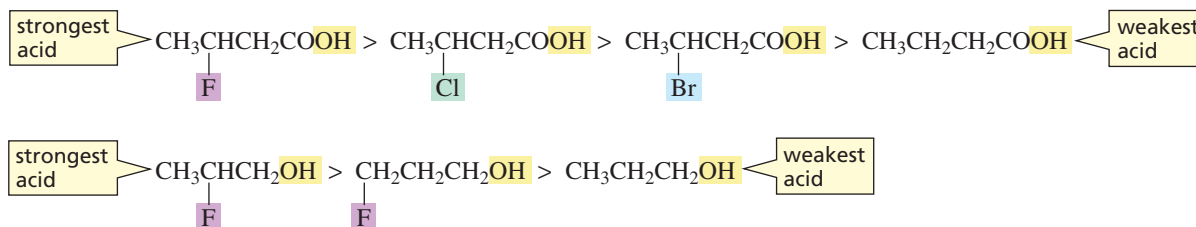
Which is a stronger acid? Why?

$CH_3C(=O)OH$ or $CH_3S(=O)_2OH$

2.9 A SUMMARY OF THE FACTORS THAT DETERMINE ACID STRENGTH

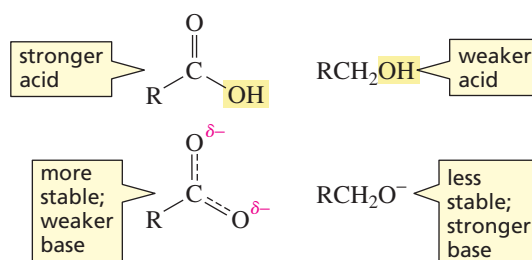
We have seen that the strength of an acid depends on five factors: the *size* of the atom to which the hydrogen is attached, the *electronegativity* of the atom to which the hydrogen is attached, the *hybridization* of the atom to which the hydrogen is attached, *inductive electron withdrawal*, and *electron delocalization*. All five factors affect acidity by affecting the stability of the conjugate base.

1. **Size:** As the atom attached to the hydrogen increases in size (going down a column of the periodic table), the strength of the acid increases.
2. **Electronegativity:** As the atom attached to the hydrogen increases in electronegativity (going from left to right across a row of the periodic table), the strength of the acid increases.

3. **Hybridization:** The electronegativity of an atom changes with hybridization as follows: *sp* > sp^2 > sp^3. Because an *sp* carbon is the most electronegative, a hydrogen attached to an *sp* carbon is the most acidic, and a hydrogen attached to an sp^3 carbon is the least acidic.

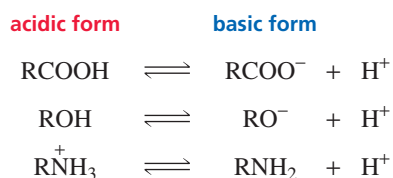
strongest acid → $HC{\equiv}CH$ > $H_2C{=}CH_2$ > CH_3CH_3 ← weakest acid

(*sp*) (sp^2) (sp^3)

4. **Inductive electron withdrawal:** An electron-withdrawing group increases the strength of an acid. As the electronegativity of the electron-withdrawing group increases, or as an electron-withdrawing atom moves closer to the acidic hydrogen, the strength of the acid increases.

5. **Electron delocalization:** An acid whose conjugate base has delocalized electrons is more acidic than a similar acid whose conjugate base has only localized electrons.

stronger acid: $RC(=O)OH$ — RCH_2OH: weaker acid

more stable; weaker base: $RC(=O^{\delta-})O^{\delta-}$ — RCH_2O^-: less stable; stronger base

2.10 HOW pH AFFECTS THE STRUCTURE OF AN ORGANIC COMPOUND

Whether a given acid will lose a proton in an aqueous solution depends on both the pK_a of the acid and the pH of the solution.

acidic form		basic form
$RCOOH$	$\rightleftharpoons$	$RCOO^- + H^+$
ROH	$\rightleftharpoons$	$RO^- + H^+$
$R\overset{+}{N}H_3$	$\rightleftharpoons$	$RNH_2 + H^+$

- A compound will exist primarily in its acidic form (with its proton) when the pH of the solution is less than the compound's pK_a value.
- A compound will exist primarily in its basic form (without its proton) when the pH of the solution is greater than the compound's pK_a value.
- When the pH of a solution equals the pK_a of the compound, the concentration of the compound in its acidic form will be the same as the concentration of the compound in its basic form.

In other words, *compounds exist primarily in their acidic forms in solutions that are more acidic than their* pK_a *values and primarily in their basic forms in solutions that are more basic than their* pK_a *values.*

PROBLEM-SOLVING STRATEGY

Determining the Structure at a Particular pH

Write the form in which the following compounds will predominate in a solution at pH 5.5:

a. CH_3CH_2OH (pK_a = 15.9) **b.** $CH_3CH_2\overset{+}{O}H_2$ (pK_a = −2.5) **c.** $CH_3\overset{+}{N}H_3$ (pK_a = 11.0)

To answer this kind of question, we need to compare the pH of the solution with the pK_a value of the compound's dissociable proton.

a. The pH of the solution is more acidic (5.5) than the pK_a value of the compound (15.9). Therefore, the compound will exist primarily as CH_3CH_2OH (with its proton).
b. The pH of the solution is more basic (5.5) than the pK_a value of the compound (−2.5). Therefore, the compound will exist primarily as CH_3CH_2OH (without its proton).
c. The pH of the solution is more acidic (5.5) than the pK_a value of the compound (11.0). Therefore, the compound will exist primarily as $CH_3\overset{+}{N}H_3$ (with its proton).

Now use the skill you have just learned to solve Problem 31.

PROBLEM 31♦

For each of the following compounds (shown in their acidic forms), write the form that will predominate in a solution of pH = 5.5:

a. CH_3COOH (pK_a = 4.76)
b. $CH_3CH_2\overset{+}{N}H_3$ (pK_a = 11.0)
c. H_3O^+ (pK_a = −1.7)
d. HBr (pK_a = −9)
e. $^+NH_4$ (pK_a = 9.4)
f. HC≡N (pK_a = 9.1)
g. HNO_2 (pK_a = 3.4)
h. HNO_3 (pK_a = −1.3)

PROBLEM 32♦ Solved

a. Indicate whether a carboxylic acid (RCOOH) with a pK_a value of 4.5 will have more charged molecules or more neutral molecules in a solution with the following pH:

1. pH = 1 **3.** pH = 5 **5.** pH = 10
2. pH = 3 **4.** pH = 7 **6.** pH = 13

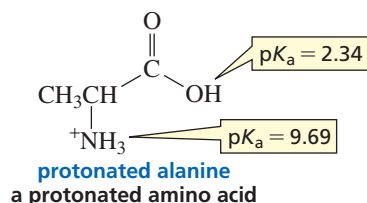
b. Answer the same question for a protonated amine ($R\overset{+}{N}H_3$) with a pK_a value of 9.
c. Answer the same question for an alcohol (ROH) with a pK_a value of 15.

You are what you're in: a compound will be mostly in the acidic form in an acidic solution (pH < pK_a) and mostly in the basic form in a basic solution (pH > pK_a).

Solution to 32a First determine whether the compound is charged or neutral in its acidic form and charged or neutral in its basic form: a carboxylic acid is neutral in its acidic form (RCOOH) and charged in its basic form ($RCOO^-$). Then compare the pH and pK_a values and remember that if the pH of the solution is less than the pK_a value of the compound, then more molecules will be in the acidic form, but if the pH is greater than the pK_a value of the compound, then more molecules will be in the basic form. Therefore, at pH = 1 and 3, there will be more neutral molecules, and at pH = 5, 7, 10, and 13, there will be more charged molecules.

PROBLEM 33

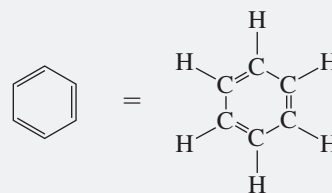
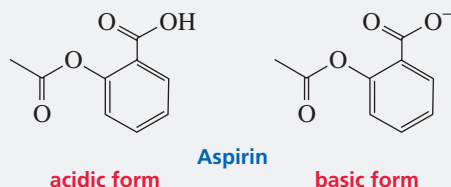
A naturally occurring amino acid such as alanine has a group that is a carboxylic acid and a group that is a protonated amine. The pK_a values of the two groups are shown.

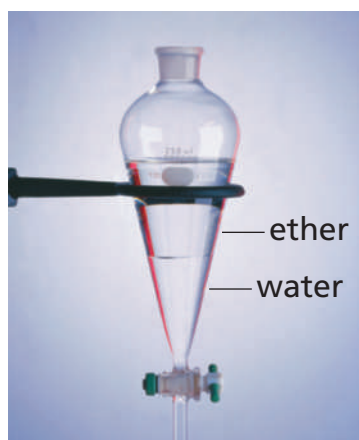
protonated alanine
a protonated amino acid

a. If the pK_a value of carboxylic acid such as acetic acid is about 5 (see Table 2.1), then why is the pK_a value of the carboxylic acid group of alanine so much lower?
b. Draw the structure of alanine in a solution at pH = 0.
c. Draw the structure of alanine in a solution at physiological pH (pH 7.4).
d. Draw the structure of alanine in a solution at pH = 12.
e. Is there a pH at which alanine will be uncharged (that is, neither group will have a charge)?

Aspirin Must Be in Its Basic Form to Be Physiologically Active

Aspirin has been used to treat fever, mild pain, and inflammation since it first became commercially available in 1899. It was the first drug to be tested clinically before it was marketed (Section 6.10). Currently one of the most widely used drugs in the world, aspirin is one of a group of over-the-counter drugs known as NSAIDs (nonsteroidal anti-inflammatory drugs).

Aspirin is a carboxylic acid. When we look at the reaction responsible for its fever-reducing, pain-reducing, and anti-inflammatory properties in Section 11.10, we will see that the carboxylic acid group must be in its basic form to be physiologically active.

acidic form — Aspirin — basic form

The carboxylic acid group has a pK_a value of ~5. Therefore, it will be in its acidic form while it is in the stomach (pH = 1–2.5). The uncharged acidic form can pass easily through membranes, whereas the negatively charged basic form cannot. In the environment of the cell (pH 7.4), the drug will be in its active basic form and will therefore be able to carry out the reaction that reduces fever, pain, and inflammation.

The undesirable side effects of aspirin (ulcers, stomach bleeding) led to the development of other NSAIDs (page 122). Aspirin also has been linked to the development of Reye's syndrome, a rare but serious disease that affects children who are recovering from a viral infection such as a cold, the flu, or chicken pox. Therefore, it is now recommended that aspirin not be given to anyone under the age of 16 who has a fever-producing illness.

PROBLEM 34♦ Solved

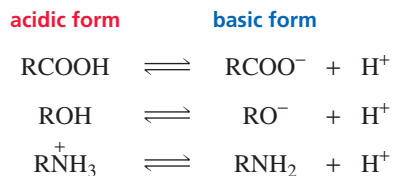
Water and ether are immiscible liquids. Charged compounds dissolve in water and uncharged compounds dissolve in ether (Section 3.7). Given that $C_6H_{11}COOH$ has a pK_a = 4.8 and $C_6H_{11}\overset{+}{N}H_3$ has a pK_a = 10.7, answer the following:

a. What pH would you make the water layer in order to cause both compounds to dissolve in it?
b. What pH would you make the water layer in order to cause the acid to dissolve in the water layer and the amine to dissolve in the ether layer?
c. What pH would you make the water layer in order to cause the acid to dissolve in the ether layer and the amine to dissolve in the water layer?

Solution to 34a A compound has to be charged in order to dissolve in the water layer. The carboxylic acid will be charged in its basic form—it will be a carboxylate ion. For > 99% of the carboxylic acid to be in its basic form, the pH must be two units *greater* than the pK_a of the compound. Thus, the water should have a pH > 6.8. The amine will be charged in its acidic form—it will be an ammonium ion. For > 99% of the amine to be in its acidic form, the pH must be two units *less* than the pK_a value of the ammonium ion. Thus, the water should have a pH < 8.7. Both compounds will dissolve in the water layer if its pH is 6.8–8.7. A pH in the middle of the range (for example, pH = 7.7) would be a good choice.

2.11 BUFFER SOLUTIONS

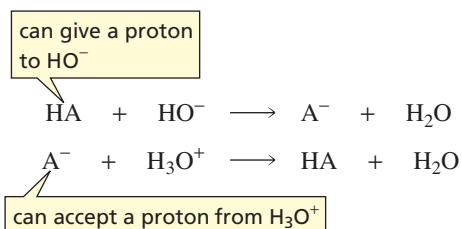
A solution of a weak acid (HA) and its conjugate base (A^-) is called a **buffer solution.** The components of three possible buffer solutions are shown here.

acidic form		basic form
RCOOH	$\rightleftharpoons$	$RCOO^- + H^+$
ROH	$\rightleftharpoons$	$RO^- + H^+$
$R\overset{+}{N}H_3$	$\rightleftharpoons$	$RNH_2 + H^+$

A buffer solution will maintain nearly constant pH when small amounts of acid or base are added to it, because the weak acid can give a proton to any HO^- added to the solution, and its conjugate base can accept any H^+ that is added to the solution.

can give a proton to HO^-

$$HA + HO^- \longrightarrow A^- + H_2O$$

$$A^- + H_3O^+ \longrightarrow HA + H_2O$$

can accept a proton from H_3O^+

PROBLEM 35♦

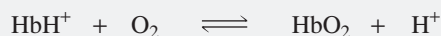
Write the equation that shows how a buffer made by dissolving CH_3COOH and $CH_3COO^-Na^+$ in water prevents the pH of a solution from changing appreciably when

a. a small amount of H^+ is added to the solution.
b. a small amount of HO^- is added to the solution.

Blood: A Buffered Solution

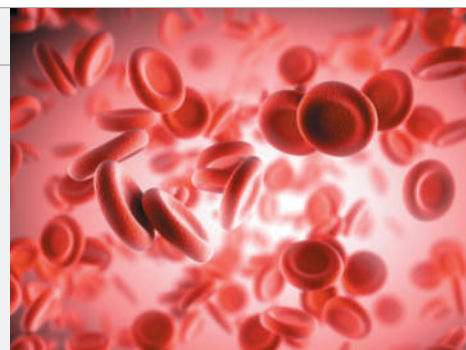
Blood is the fluid that transports oxygen to all the cells of the human body. The normal pH of human blood is ~7.4. Death will result if this pH decreases to less than ~6.8 or increases to greater than ~8.0 for even a few seconds.

Oxygen is carried to cells by a protein in the blood called hemoglobin (HbH^+). When hemoglobin binds O_2, hemoglobin loses a proton, which would make the blood more acidic if it did not contain a buffer to maintain its pH.

$$HbH^+ + O_2 \rightleftharpoons HbO_2 + H^+$$

A carbonic acid/bicarbonate (H_2CO_3/HCO_3^-) buffer controls the pH of blood. An important feature of this buffer is that carbonic acid decomposes to CO_2 and H_2O, as shown below:

$$\underset{\text{bicarbonate}}{HCO_3^-} + H^+ \rightleftharpoons \underset{\text{carbonic acid}}{H_2CO_3} \rightleftharpoons CO_2 + H_2O$$

During exercise our metabolism speeds up, producing large amounts of CO_2. The increased concentration of CO_2 shifts the equilibrium between carbonic acid and bicarbonate to the left, which increases the concentration of H^+. Significant amounts of lactic acid are also produced during exercise, which further increases the concentration of H^+. Receptors in the brain respond to the increased concentration of H^+ by triggering a reflex that increases the rate of breathing. Hemoglobin then releases more oxygen to the cells and more CO_2 is eliminated by exhalation. Both processes decrease the concentration of H^+ in the blood by shifting the equilibrium of the top reaction to the left and the equilibrium of the bottom reaction to the right.

Thus, any disorder that decreases the rate and depth of ventilation, such as emphysema, will decrease the pH of the blood—a condition called acidosis. In contrast, any excessive increase in the rate and depth of ventilation, as with hyperventilation due to anxiety, will increase the pH of blood—a condition called alkalosis.

PROBLEM 36 Solved

You are planning to carry out a reaction that produces hydroxide ion. In order for the reaction to take place at a constant pH, it will be buffered at pH = 4.2. Would it be better to use a formic acid/formate buffer or an acetic acid/acetate buffer? (Note: the pK_a of formic acid = 3.75 and the pK_a of acetic acid = 4.76.)

Solution Constant pH will be maintained because the hydroxide ion produced in the reaction will remove a proton from the acidic form of the buffer. Thus, the better choice of buffer is the one that has the highest concentration of buffer in the acidic form at pH = 4.2. Because formic acid's pK_a is 3.75, the majority of the buffer will be in the basic form at pH = 4.2. Acetic acid, with $pK_a = 4.76$, will have more buffer in the acidic form than in the basic form. Thus, it would be better to use acetic acid/acetate buffer for your reaction.

PROBLEM 37♦

What products are formed when each of the following reacts with HO^-?

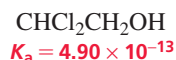
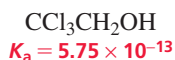
a. CH_3OH **b.** $^+NH_4$ **c.** $CH_3\overset{+}{N}H_3$ **d.** CH_3COOH

SOME IMPORTANT THINGS TO REMEMBER

- An **acid** is a species that donates a proton; a **base** is a species that accepts a proton.
- A **Lewis acid** is a species that accepts a share in an electron pair; a **Lewis base** is a species that donates a share in an electron pair.
- **Acidity** is a measure of the tendency of a compound to lose a proton.
- **Basicity** is a measure of a compound's affinity for a proton.
- A strong base has a high affinity for a proton; a weak base has a low affinity for a proton.
- The stronger the acid, the weaker its conjugate base.
- The strength of an acid is given by the **acid dissociation constant** (K_a).
- The stronger the acid, the smaller its pK_a value.
- Approximate pK_a values are as follows: protonated alcohols, protonated carboxylic acids, protonated water < 0; carboxylic acids ~5; protonated amines ~10; alcohols and water ~15.
- The **pH** of a solution indicates the concentration of protons in the solution; the smaller the pH, the more acidic the solution.
- In **acid–base reactions,** the equilibrium favors formation of the weaker acid.
- Curved arrows indicate the bonds that are broken and formed as reactants are converted into products.
- The strength of an acid is determined by the stability of its conjugate base: the more stable (weaker) the base, the stronger its conjugate acid.
- When atoms are similar in size, the strongest acid will have its hydrogen attached to the more electronegative atom.
- When atoms are very different in size, the strongest acid will have its hydrogen attached to the larger atom.
- Hybridization affects acidity because an *sp* hybridized atom is more electronegative than an sp^2 hybridized atom, which is more electronegative than an sp^3 hybridized atom.
- **Inductive electron withdrawal** increases acidity: the more electronegative the electron-withdrawing group and the closer it is to the acidic hydrogen, the stronger is the acid.
- **Delocalized electrons** (electrons that are shared by more than two atoms) stabilize a compound.
- A **resonance hybrid** is a composite of the **resonance contributors,** structures that differ only in the location of their π electrons and lone-pair electrons.
- A compound exists primarily in its acidic form (with its proton) in solutions more acidic than its pK_a value and primarily in its basic form (without its proton) in solutions more basic than its pK_a value.
- A **buffer solution** contains both a weak acid and its conjugate base.

PROBLEMS

38. a. List the following alcohols in order from strongest acid to weakest acid:

CCl_3CH_2OH	CH_2ClCH_2OH	$CHCl_2CH_2OH$
$K_a = 5.75 \times 10^{-13}$	$K_a = 1.29 \times 10^{-13}$	$K_a = 4.90 \times 10^{-13}$

b. Explain the relative acidities.

39. Which is a stronger base?

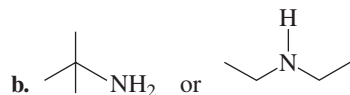
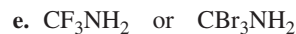
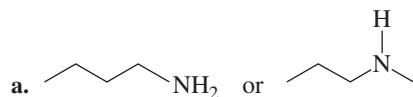
a.

c. I^- or Cl^-

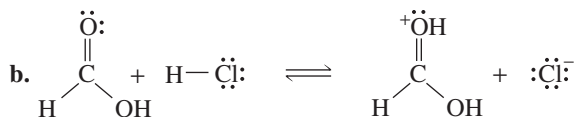
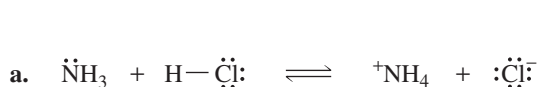
e. CF_3NH_2 or CBr_3NH_2

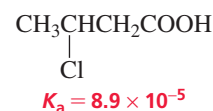
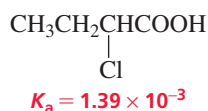
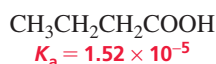
b.

d. $CH_3CH_2COO^-$ or $CHCl_2COO^-$

f. CH_3^- or CH_2CH^-

40. Draw curved arrows to show where the electrons start from and where they end up in the following reactions:

a. $\ddot{N}H_3 + H-\ddot{\underset{..}{Cl}}: \rightleftharpoons {}^{+}NH_4 + :\ddot{\underset{..}{Cl}}:^-$

b. $H-C(=\ddot{O}:)-OH + H-\ddot{\underset{..}{Cl}}: \rightleftharpoons H-C(={}^{+}\ddot{O}H)-OH + :\ddot{\underset{..}{Cl}}:^-$

41. a. List the following carboxylic acids in order from strongest acid to weakest acid:

$CH_3CH_2CH_2COOH$	$CH_3CH_2CH(Cl)COOH$	$ClCH_2CH_2CH_2COOH$	$CH_3CH(Cl)CH_2COOH$
$K_a = 1.52 \times 10^{-5}$	$K_a = 1.39 \times 10^{-3}$	$K_a = 2.96 \times 10^{-5}$	$K_a = 8.9 \times 10^{-5}$

b. How does the presence of an electronegative substituent such as Cl affect the acidity of a carboxylic acid?

c. How does the location of the substituent affect the acidity of the carboxylic acid?

42. For the following compound,

a. draw its conjugate acid. **b.** draw its conjugate base.

H_2NCH_2COOH

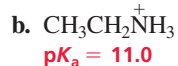
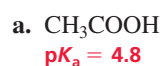
43. List the following compounds in order from strongest acid to weakest acid:

CH_4 CH_3COOH CH_3OH $CHCl_2OH$

44. For each of the following compounds, draw the form in which it will predominate at pH = 3, pH = 6, pH = 10, and pH = 14:

a. CH_3COOH, $pK_a = 4.8$

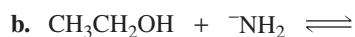
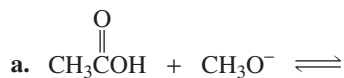
b. $CH_3CH_2\overset{+}{N}H_3$, $pK_a = 11.0$

c. CF_3CH_2OH, $pK_a = 12.4$

45. Give the products of the following acid–base reactions, and indicate whether reactants or products are favored at equilibrium (use the pK_a values that are given in Section 2.3):

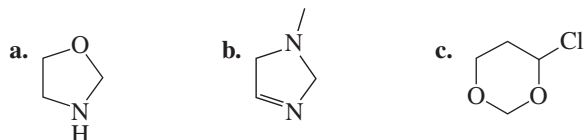
a. $CH_3\overset{O}{\overset{\|}{C}}OH + CH_3O^- \rightleftharpoons$

c. $CH_3\overset{O}{\overset{\|}{C}}OH + CH_3NH_2 \rightleftharpoons$

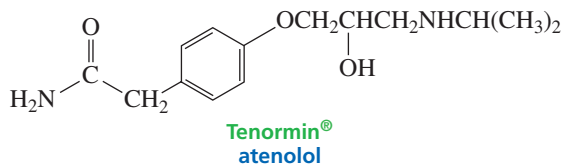
b. $CH_3CH_2OH + {}^-NH_2 \rightleftharpoons$

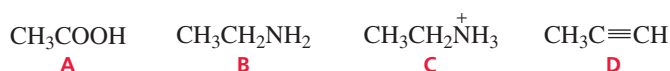
d. $CH_3CH_2OH + HCl \rightleftharpoons$

46. a. List the following alcohols in order from strongest acid to weakest acid.
b. Explain the relative acidities.

$CH_2{=}CHCH_2OH$ $CH_3CH_2CH_2OH$ $HC{\equiv}CCH_2OH$

47. For each compound, indicate the atom that is most likely to be protonated.

48. Tenormin, a member of the group of drugs known as beta-blockers, is used to treat high blood pressure and improve survival after a heart attack. It works by slowing down the heart in order to reduce its workload. Which hydrogen in Tenormin is the most acidic?

H_2N–C(=O)–CH_2–C_6H_4–$OCH_2CH(OH)CH_2NHCH(CH_3)_2$

Tenormin®
atenolol

49. From which acids can HO^- remove a proton in a reaction that favors product formation?

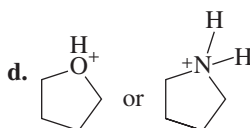
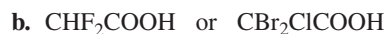
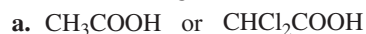
CH_3COOH	$CH_3CH_2NH_2$	$CH_3CH_2\overset{+}{N}H_3$	$CH_3C{\equiv}CH$
A	**B**	**C**	**D**

50. You are planning to carry out a reaction that produces protons. The reaction will be buffered at pH = 10.5. Would it be better to use a protonated methylamine/methylamine buffer or a protonated ethylamine/ethylamine buffer? (pK_a of protonated methylamine = 10.7; pK_a of protonated ethylamine = 11.0)

51. Which is a stronger acid?

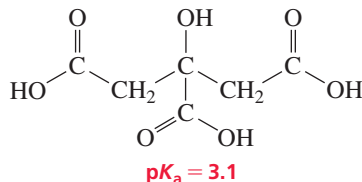
a. CH_3COOH or $CHCl_2COOH$

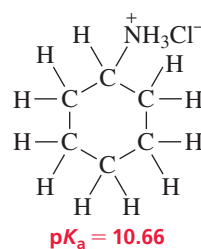
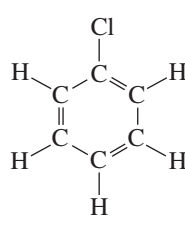
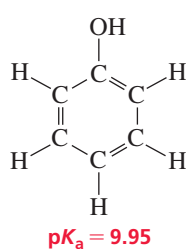
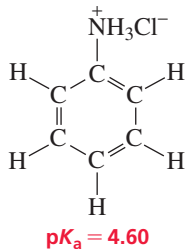
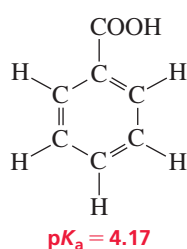
b. CHF_2COOH or $CBr_2ClCOOH$

c. CH_3COOH or $CH_3CH_2CH_2CH_2CH_2COOH$

d. protonated tetrahydrofuran ($\overset{+}{O}$–H) or protonated pyrrolidine ($\overset{+}{N}H_2$)

52. Citrus fruits are rich in citric acid, a compound with three COOH groups. Explain why the pK_a (for the COOH group in the center of the molecule) is lower than the pK_a of acetic acid (4.76).

$HOOC–CH_2–C(OH)(COOH)–CH_2–COOH$

pK_a = 3.1

53. Carbonic acid has a pK_a of 6.1 at physiological temperature. Is the carbonic acid/bicarbonate buffer system that maintains the pH of the blood at 7.4 better at neutralizing excess acid or excess base?

54. How could you separate a mixture of the following compounds? The reagents available to you are water, ether, 1.0 M HCl, and 1.0 M NaOH. (*Hint:* See Problem 34.)

C_6H_5COOH	$C_6H_5\overset{+}{N}H_3Cl^-$	C_6H_5OH	C_6H_5Cl	$C_6H_{11}\overset{+}{N}H_3Cl^-$
pK_a = 4.17	**pK_a = 4.60**	**pK_a = 9.95**		**pK_a = 10.66**

ACIDS AND BASES

TUTORIAL

Enhanced by MasteringChemistry®

This tutorial is designed to give you practice solving problems based on some of the concepts you learned in Chapter 2. Most of the concepts are given here without explanation because full explanations can be found in Chapter 2.

An Acid and Its Conjugate Base

An acid is a species that can lose a proton (the Brønsted–Lowry definition). When an acid loses a proton (H^+), it forms its conjugate base. When the proton comes off the acid, the conjugate base retains the electron pair that attached the proton to the acid.

$CH_3C(=O)\ddot{O}H$ (acid) → $CH_3C(=O)\ddot{O}^-$ (conjugate base) + H^+ (a proton)

Often, the lone pairs and bonding electrons are not shown.

CH_3COOH (acid) → CH_3COO^- (conjugate base) + H^+

$CH_3\overset{+}{O}H_2$ (acid) → CH_3OH (conjugate base) + H^+

Notice that a neutral acid forms a negatively charged conjugate base, whereas a positively charged acid forms a neutral conjugate base. (In each case, the charge *decreases* by one because the acid *loses* H^+.)

PROBLEM 1 Draw the conjugate base of each of the following acids:

a. CH_3OH **b.** $CH_3\overset{+}{N}H_3$ **c.** CH_3NH_2 **d.** H_3O^+ **e.** H_2O

A Base and Its Conjugate Acid

A base is a species that can gain a proton (the Brønsted–Lowry definition). When a base gains a proton (H^+), it forms its conjugate acid. In order to gain a proton, a base must have a lone pair that it can use to form a new bond with the proton.

$CH_3\ddot{O}^-$ (base) + H^+ → $CH_3\ddot{O}-H$ (conjugate acid)

Often, the lone pairs and bonding electrons are not shown.

Notice that a negatively charged base forms a neutral conjugate acid, whereas a neutral base forms a positively charged conjugate acid. (In each case, the charge *increases* by one because the compound *gains* H^+.)

PROBLEM 2 Draw the conjugate acid of each of the following bases:

a. H_2O **b.** HO^- **c.** CH_3OH **d.** NH_3 **e.** Cl^-

Acid–Base Reactions

An acid cannot lose a proton unless a base is present to accept the proton. Therefore, an acid always reacts with a base. The reaction of an acid with a base is called an acid–base reaction or a proton transfer reaction. Acid–base reactions are reversible reactions.

$$CH_3C(=O)OH + H_2O \rightleftharpoons CH_3C(=O)O^- + H_3O^+$$

acid / conjugate acid; base / conjugate base; conjugate base / base; conjugate acid / acid

Notice that an acid reacts with a base in the forward direction (blue labels) and an acid reacts with a base in the reverse direction (red labels).

The Products of an Acid–Base Reaction

Both CH_3COOH and H_2O in the preceding reaction have protons that can be lost (that is, both can act as acids), and both have lone pairs that can form a bond with a proton (that is, both can act as bases). How do we know which reactant will lose a proton and which will gain a proton? We can determine this by comparing the pK_a values of the two reactants; these values are 4.8 for CH_3COOH and 15.7 for H_2O. The stronger acid (the one with the lower pK_a value) will be the one that acts as an acid (it will lose a proton). The other reactant will act as a base (it will gain a proton).

$$\underset{pK_a = 4.8}{CH_3C(=O)OH} + \underset{pK_a = 15.7}{H_2O} \rightleftharpoons CH_3C(=O)O^- + H_3O^+$$

PROBLEM 3 Draw the products of the following acid–base reactions:

a. $CH_3\overset{+}{N}H_3 + H_2O$ **c.** $CH_3\overset{+}{N}H_3 + HO^-$

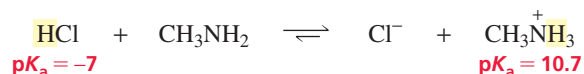
b. $HBr + CH_3OH$ **d.** $CH_3NH_2 + CH_3OH$

The Position of Equilibrium

Whether an acid–base reaction favors formation of the products or formation of the reactants can be determined by comparing the pK_a value of the acid that loses a proton in the forward direction with the pK_a value of the acid that loses a proton in the reverse direction. The equilibrium will favor the reaction of the stronger acid to form the weaker acid. The following reaction favors formation of the reactants, because $CH_3\overset{+}{O}H_2$ is a stronger acid than CH_3COOH.

$$\underset{pK_a = 4.8}{CH_3C(=O)OH} + CH_3OH \rightleftharpoons CH_3C(=O)O^- + \underset{pK_a = -1.7}{CH_3\overset{+}{O}H_2}$$

The next reaction favors formation of the products, because HCl is a stronger acid than $CH_3\overset{+}{N}H_3$.

$$\underset{pK_a = -7}{HCl} + CH_3NH_2 \rightleftharpoons Cl^- + \underset{pK_a = 10.7}{CH_3\overset{+}{N}H_3}$$

PROBLEM 4 Which of the reactions in Problem 3 favor formation of the reactants, and which favor formation of the products? (The pK_a values can be found in Sections 2.3 and 2.6.)

Relative Acid Strengths When the Proton Is Attached to Atoms Similar in Size

The atoms in the second row of the periodic table are similar in size, but they have different electronegativities.

relative electronegativities

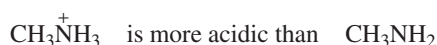
$$C < N < O < F$$ (most electronegative)

When acids have protons attached to atoms similar in size, the strongest acid is the one with the proton attached to the more electronegative atom. The relative acid strengths are as follows:

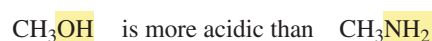
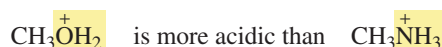
(strongest acid) $HF > H_2O > NH_3 > CH_4$ (weakest acid)

A positively charged atom is more electronegative than the same atom when it is neutral. Therefore,

$CH_3\overset{+}{N}H_3$ is more acidic than CH_3NH_2

$CH_3\overset{+}{O}H_2$ is more acidic than CH_3OH

When the relative strengths of two acids are determined by comparing the electronegativities of the atoms to which the protons are attached, both acids must possess the same charge. Therefore,

$CH_3\overset{+}{O}H_2$ is more acidic than $CH_3\overset{+}{N}H_3$

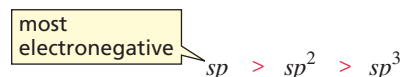
CH_3OH is more acidic than CH_3NH_2

PROBLEM 5 Which is the stronger acid?

a. CH_3OH or CH_3CH_3 **c.** CH_3NH_2 or HF

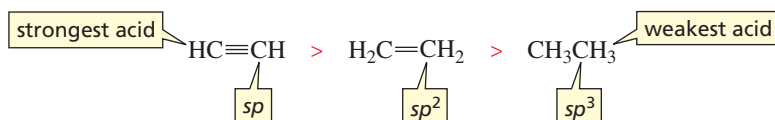
b. CH_3OH or HF **d.** CH_3NH_2 or CH_3OH

The Effect of Hybridization on Acidity

The electronegativity of an atom depends on its hybridization.

(most electronegative) $sp > sp^2 > sp^3$

Once again, the stronger acid will have its proton attached to the more electronegative atom. Thus, the relative acid strengths are as follows:

(strongest acid) $HC{\equiv}CH > H_2C{=}CH_2 > CH_3CH_3$ (weakest acid)

(sp) (sp^2) (sp^3)

PROBLEM 6 Which is the stronger acid?

a. CH_3CH_3 or $HC{\equiv}CH$ **b.** $H_2C{=}CH_2$ or $HC{\equiv}CH$ **c.** $H_2C{=}CH_2$ or CH_3CH_3

Relative Acid Strengths When the Proton Is Attached to Atoms Very Different in Size

The atoms in a column of the periodic table become considerably larger as you go down the column.

largest halide ion $I^- > Br^- > Cl^- > F^-$ smallest halide ion

When comparing two acids with protons attached to atoms that are very different in size, the stronger acid is the one attached to the larger atom. Thus, the relative acid strengths are as follows:

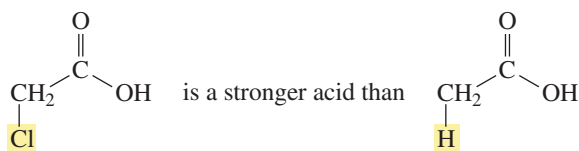
strongest acid $HI > HBr > HCl > HF$ weakest acid

PROBLEM 7 Which is the stronger acid? (*Hint*: You can use the periodic table at the back of this book.)

a. HCl or HBr **b.** CH_3OH or CH_3SH **c.** HF or HCl **d.** H_2S or H_2O

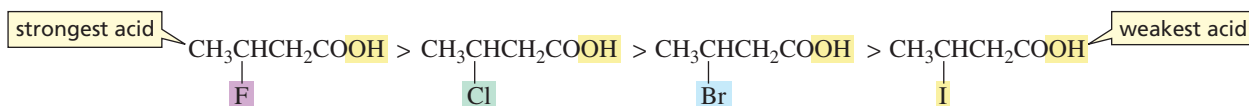
The Effect of Inductive Electron Withdrawal on Acidity

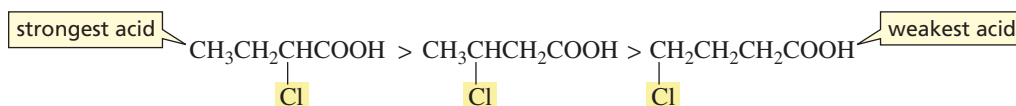
Replacing a hydrogen with an electronegative substituent—one that pulls bonding electrons toward itself—increases the strength of the acid.

$ClCH_2C(=O)OH$ is a stronger acid than $HCH_2C(=O)OH$

The halogens have the following relative electronegativities:

most electronegative $F > Cl > Br > I$ least electronegative

The more electronegative the substituent that replaces a hydrogen, the stronger the acid. Thus, the relative acid strengths are as follows:

strongest acid $CH_3CH(F)CH_2COOH > CH_3CH(Cl)CH_2COOH > CH_3CH(Br)CH_2COOH > CH_3CH(I)CH_2COOH$ weakest acid

The closer the electronegative substituent is to the group that loses a proton, the stronger the acid will be. Thus, the relative acid strengths are as follows:

strongest acid $CH_3CH_2CH(Cl)COOH > CH_3CH(Cl)CH_2COOH > CH_2(Cl)CH_2CH_2COOH$ weakest acid

PROBLEM 8 Which is the stronger acid?

a. $ClCH_2CH_2OH$ or FCH_2CH_2OH

b. $CH_3CH_2OCH_2OH$ or $CH_3OCH_2CH_2OH$

c. $CH_3C(=O)CH_2CH_2OH$ or $CH_3CH_2C(=O)CH_2OH$

Relative Base Strengths

Strong bases readily share their electrons with a proton. In other words, the conjugate acid of a *strong* base is a *weak* acid because it does not readily lose a proton. This allows us to say, *the stronger the base, the weaker its conjugate acid* (or *the stronger the acid, the weaker its conjugate base*).

For example, which is the stronger base?

a. CH_3O^- or CH_3NH^- **b.** $HC{\equiv}C^-$ or $CH_3\bar{C}H_2$

In order to answer the question, first compare their conjugate acids:

a. CH_3OH is a stronger acid than CH_3NH_2 (because O is more electronegative than N). Since the stronger acid has the weaker conjugate base, $CH_3\bar{N}H$ is a stronger base than CH_3O^-.

b. $HC{\equiv}CH$ is a stronger acid than CH_3CH_3 (an *sp* hybridized atom is more electronegative than an sp^3 hybridized atom). Therefore, $CH_3\bar{C}H_2$ is a stronger base.

PROBLEM 9 Which is the stronger base?

a. Br^- or I^-
b. CH_3O^- or CH_3S^-
c. $CH_3CH_2O^-$ or CH_3COO^-
d. $H_2C{=}\bar{C}H$ or $HC{\equiv}C^-$
e. $FCH_2CH_2COO^-$ or $BrCH_2CH_2COO^-$
f. $ClCH_2CH_2O^-$ or $Cl_2CHCH_2O^-$

Weak Bases Are Stable Bases

Weak bases are stable bases because they readily bear the electrons they formerly shared with a proton. Therefore, we can say, *the weaker the base, the more stable it is.* We can also say, *the stronger the acid, the more stable (the weaker) its conjugate base.*

For example, which is a more stable base, Cl^- or Br^-?

In order to determine this, first compare their conjugate acids:
HBr is a stronger acid than HCl (because Br is larger than Cl). Therefore, Br^- is a more stable (weaker) base.

PROBLEM 10 Which is the more stable base?

a. Br^- or I^-
b. CH_3O^- or CH_3S^-
c. $CH_3CH_2O^-$ or CH_3COO^-
d. $H_2C{=}\bar{C}H$ or $HC{\equiv}C^-$
e. $FCH_2CH_2COO^-$ or $BrCH_2CH_2COO^-$
f. $ClCH_2CH_2O^-$ or $Cl_2CHCH_2O^-$

Electron Delocalization Stabilizes a Base

If a base has localized electrons, then the negative charge that results when the base's conjugate acid loses a proton will belong to one atom. On the other hand, if a base has delocalized electrons, then the negative charge that results when the base's conjugate acid loses a proton will be shared by two (or more) atoms. A base with delocalized electrons is more stable than a similar base with localized electrons.

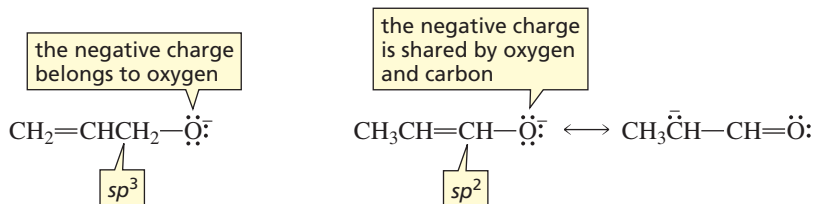
the negative charge belongs to oxygen

$CH_2{=}CHCH_2{-}\ddot{O}{:}^-$

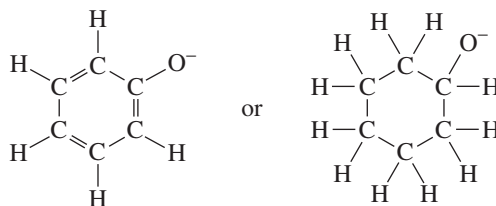
sp^3

the negative charge is shared by oxygen and carbon

$CH_3CH{=}CH{-}\ddot{O}{:}^- \longleftrightarrow CH_3\bar{C}H{-}CH{=}\ddot{O}{:}$

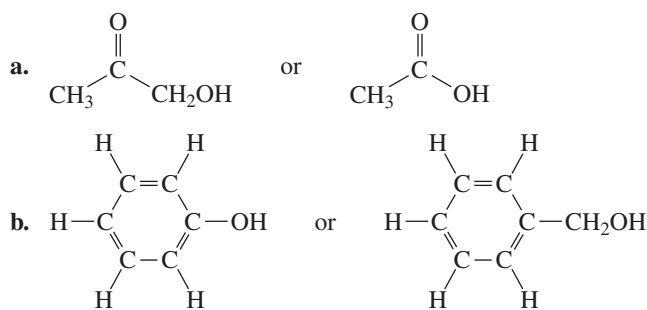
sp^2

How do we know whether a base has delocalized atoms? If the electrons left behind, when the base's conjugate acid loses a proton, are on an atom that is singly bonded to an sp^3 carbon, then the electrons will belong to only one atom—that is, the electrons will be *localized.* If the electrons left behind, when the base's conjugate acid loses a proton, are on an atom that is singly bonded to an sp^2 carbon, then the electrons will be *delocalized.*

PROBLEM 11 Which is a more stable base?

[Structures: phenoxide-like benzene ring with O^- (C6H5O⁻ drawn with H atoms) or cyclohexane ring with O^- (C6H11O⁻ drawn with H atoms)]

Remembering that the more stable (weaker) base has the stronger conjugate acid, solve Problem 12.

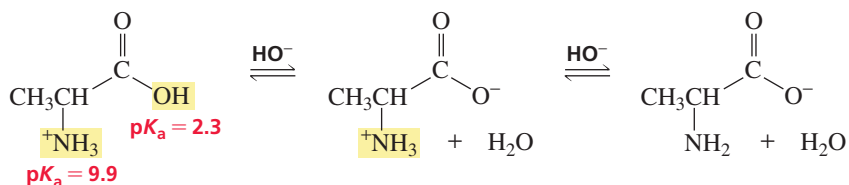
PROBLEM 12 Which is the stronger acid?

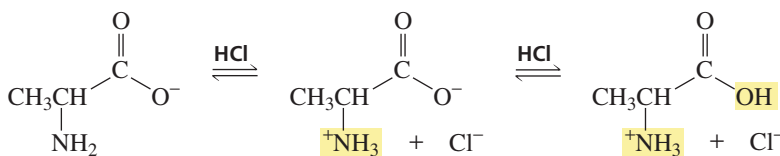
a. $CH_3C(=O)CH_2OH$ or $CH_3C(=O)OH$

b. C_6H_5OH (H—C ring with C—OH) or $C_6H_5CH_2OH$ (H—C ring with C—CH_2OH)

Compounds with More Than One Acidic Group

If a compound has two acidic groups, then a base will remove a proton from the more acidic of the two groups first. If a second equivalent of base is added, then the base will remove a proton from the less acidic group.

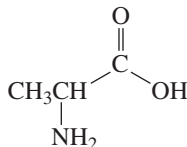
$$CH_3CH(\overset{+}{N}H_3)C(=O)OH \underset{}{\overset{HO^-}{\rightleftharpoons}} CH_3CH(\overset{+}{N}H_3)C(=O)O^- + H_2O \underset{}{\overset{HO^-}{\rightleftharpoons}} CH_3CH(NH_2)C(=O)O^- + H_2O$$

OH: $pK_a = 2.3$; $^+NH_3$: $pK_a = 9.9$

Similarly, if a compound has two basic groups, then an acid will protonate the more basic of the two groups first. If a second equivalent of acid is added, then the acid will protonate the less basic group.

$$CH_3CH(NH_2)C(=O)O^- \underset{}{\overset{HCl}{\rightleftharpoons}} CH_3CH(\overset{+}{N}H_3)C(=O)O^- + Cl^- \underset{}{\overset{HCl}{\rightleftharpoons}} CH_3CH(\overset{+}{N}H_3)C(=O)OH + Cl^-$$

PROBLEM 13

a. What species will be formed if one equivalent of HCl is added to $HOCH_2CH_2NH_2$?

b. Does the following compound exist?

$$CH_3CH(NH_2)C(=O)OH$$

The Effect of pH on Structure

Whether an acid will be in its acidic form (with its proton) or its basic form (without its proton) depends on the pK_a value of the acid and the pH of the solution:

- If $pH < pK_a$, then the compound will exist primarily in its acidic form.
- If $pH > pK_a$, then the compound will exist primarily in its basic form.

In other words, if the solution is more acidic than the pK_a value of the acid, the compound will be in its acidic form. But if the solution is more basic than the pK_a value of the acid, the compound will be in its basic form.

PROBLEM 14

a. Draw the structure of CH_3COOH ($pK_a = 4.7$) at pH = 2, pH = 7, and pH = 10.

b. Draw the structure of CH_3OH ($pK_a = 15.5$) at pH = 2, pH = 7, and pH = 10.

c. Draw the structure of $CH_3\overset{+}{N}H_3$ ($pK_a = 10.7$) at pH = 2, pH = 7, and pH = 14.

ANSWERS TO PROBLEMS ON ACIDS AND BASES

PROBLEM 1 Answer

a. CH_3O^- **b.** CH_3NH_2 **c.** $CH_3\bar{N}H$ **d.** H_2O **e.** HO^-

PROBLEM 2 Answer

a. H_3O^+ **b.** H_2O **c.** $CH_3\overset{+}{O}H_2$ **d.** $^+NH_4$ **e.** HCl

PROBLEM 3 Answer

a. $CH_3\overset{+}{N}H_3 + H_2O \rightleftharpoons CH_3NH_2 + H_3O^+$

b. $HBr + CH_3OH \rightleftharpoons Br^- + CH_3\overset{+}{O}H_2$

c. $CH_3\overset{+}{N}H_3 + HO^- \rightleftharpoons CH_3NH_2 + H_2O$

d. $CH_3NH_2 + CH_3OH \rightleftharpoons CH_3\overset{+}{N}H_3 + CH_3O^-$

PROBLEM 4 Answer

a. reactants **b.** products **c.** products **d.** reactants

PROBLEM 5 Answer

a. CH_3OH **b.** HF **c.** HF **d.** CH_3OH

PROBLEM 6 Answer

a. $HC{\equiv}CH$ **b.** $HC{\equiv}CH$ **c.** $H_2C{=}CH_2$

PROBLEM 7 Answer

a. HBr **b.** CH_3SH **c.** HCl **d.** H_2S

PROBLEM 8 Answer

a. FCH_2CH_2OH **b.** $CH_3CH_2OCH_2OH$ **c.** $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2OH$

PROBLEM 9 Answer

a. Br^- **b.** CH_3O^- **c.** $CH_3CH_2O^-$ **d.** $H_2C{=}CH^-$ **e.** $BrCH_2CH_2O^-$ **f.** $ClCH_2CH_2O^-$

PROBLEM 10 Answer

a. I^- **b.** CH_3S^- **c.** CH_3COO^- **d.** $HC{\equiv}C^-$ **e.** $FCH_2CH_2O^-$ **f.** $Cl_2CHCH_2O^-$

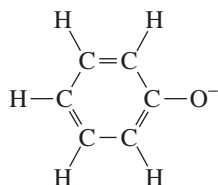
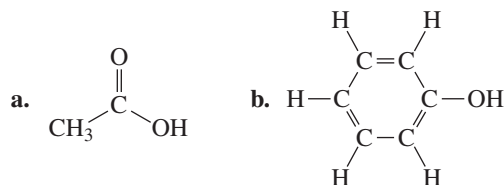
PROBLEM 11 Answer

```
      H     H
       \   /
        C=C
       /   \
  H—C       C—O⁻
      \\   //
        C—C
       /   \
      H     H
```

PROBLEM 12 Answer

a.

b.

```
      H     H
       \   /
        C=C
       /   \
  H—C       C—OH
      \\   //
        C—C
       /   \
      H     H
```

PROBLEM 13 Answer

a. $HOCH_2CH_2\overset{+}{N}H_3$

b. The compound does not exist. For it to be formed, a base would have to be able to remove a proton from a group with a pK_a = 9.9 more readily than it would remove a proton from a group with a pK_a = 2.3. This is not possible, because the lower the pK_a, the stronger the acid—that is, the more readily the group can lose a proton. In other words, a weak acid cannot lose a proton more readily than a strong acid can.

PROBLEM 14 Answer

a. CH_3COOH at pH = 2, because pH < pK_a
CH_3COO^- at pH = 7 and 10, because pH > pK_a

b. CH_3OH at pH = 2, 7, and 10, because pH < pK_a

c. $CH_3\overset{+}{N}H_3$ at pH = 2 and 7, because pH < pK_a
CH_3NH_2 at pH = 14, because pH > pK_a

MasteringChemistry® for Organic Chemistry

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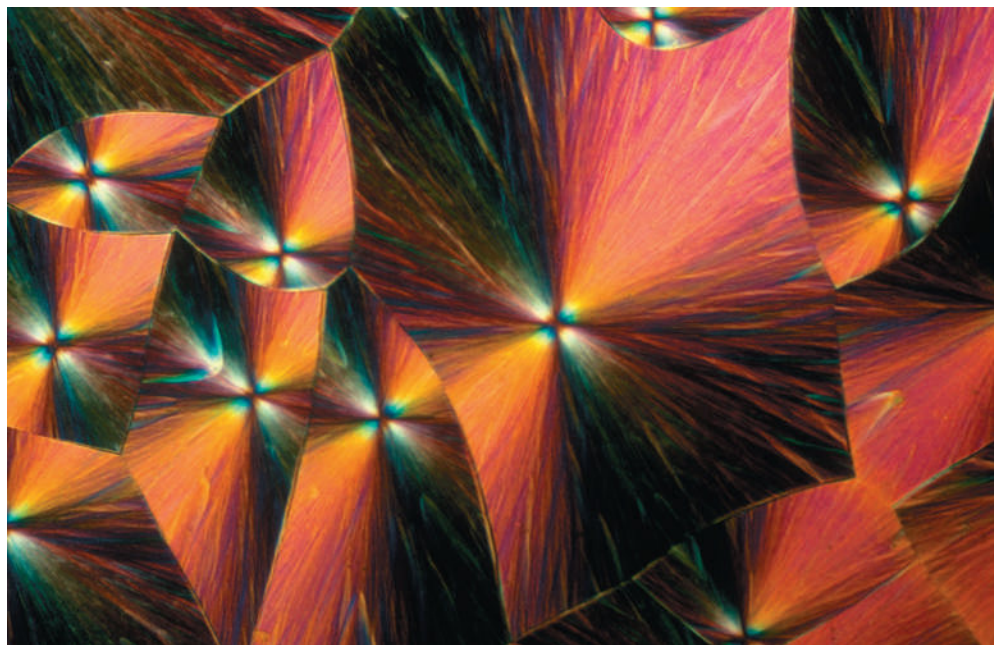
- Acids and Bases: Factors that Influence Acid Strength
- Acids and Bases: Predicting the Position of Equilibrium
- Acids and Bases: Definitions

3 An Introduction to Organic Compounds

Nomenclature, Physical Properties, and Representation of Structure

cholesterol crystals

The material in this chapter explains why drugs with similar physiological effects have similar structures, how high cholesterol is treated clinically, why fish is served with lemon, how the octane number of gasoline is determined, and why starch (a component of many of the foods we eat) and cellulose (the structural material of plants) have such different physical properties, even though both are composed only of glucose.

If we are going to talk about organic compounds, we need to know how to name them. First, we will see how *alkanes* are named because their names form the basis for the names of all other organic compounds. **Alkanes** are composed of only carbon atoms and hydrogen atoms and contain only *single bonds*. Compounds that contain only carbon and hydrogen are called **hydrocarbons.** Thus, an alkane is a hydrocarbon that has only single bonds.

Alkanes in which the carbons form a continuous chain with no branches are called **straight-chain alkanes.** The names of the four smallest straight-chain alkanes have historical roots, but the others are based on Greek numbers (Table 3.1).

If you look at the relative numbers of carbons and hydrogens in the alkanes listed in Table 3.1, you will see that the general molecular formula for an alkane is C_nH_{2n+2}, where n is any positive integer. So, if an alkane has one carbon, it must have four hydrogens; if it has two carbons, it must have six hydrogens; and so on.

We have seen that carbon forms four covalent bonds and hydrogen forms only one covalent bond (Section 1.4). This means that there is only one possible structure for an alkane with molecular formula CH_4 (methane) and only one possible structure for an alkane with molecular formula C_2H_6 (ethane). We examined the structures of these

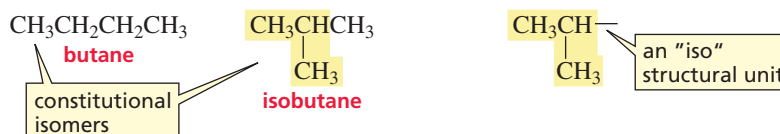
Table 3.1 Nomenclature and Physical Properties of Straight-Chain Alkanes

Number of carbons	Molecular formula	Name	Condensed structure	Boiling point (°C)	Melting point (°C)	Density[a] (g/mL)
1	CH_4	methane	CH_4	−167.7	−182.5	
2	C_2H_6	ethane	CH_3CH_3	−88.6	−183.3	
3	C_3H_8	propane	$CH_3CH_2CH_3$	−42.1	−187.7	
4	C_4H_{10}	butane	$CH_3CH_2CH_2CH_3$	−0.5	−138.3	
5	C_5H_{12}	pentane	$CH_3(CH_2)_3CH_3$	36.1	−129.8	0.5572
6	C_6H_{14}	hexane	$CH_3(CH_2)_4CH_3$	68.7	−95.3	0.6603
7	C_7H_{16}	heptane	$CH_3(CH_2)_5CH_3$	98.4	−90.6	0.6837
8	C_8H_{18}	octane	$CH_3(CH_2)_6CH_3$	125.7	−56.8	0.7026
9	C_9H_{20}	nonane	$CH_3(CH_2)_7CH_3$	150.8	−53.5	0.7177
10	$C_{10}H_{22}$	decane	$CH_3(CH_2)_8CH_3$	174.0	−29.7	0.7299

[a]Density is temperature dependent. The densities given are those determined at 20 °C $(d^{20°})$.

compounds in Section 1.7. There is also only one possible structure for an alkane with molecular formula C_3H_8 (propane).

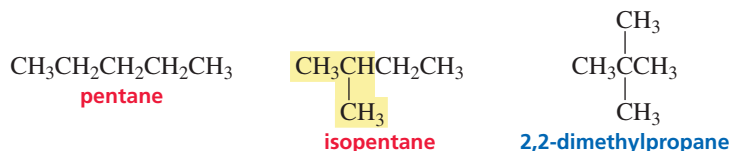
name	Kekulé structure	condensed structure	ball-and-stick model
methane	H H—C—H H	CH_4	
ethane	H H H—C—C—H H H	CH_3CH_3	
propane	H H H H—C—C—C—H H H H	$CH_3CH_2CH_3$	
butane	H H H H H—C—C—C—C—H H H H H	$CH_3CH_2CH_2CH_3$	

However, there are two possible structures for an alkane with molecular formula C_4H_{10}. In addition to butane—a straight-chain alkane—there is a branched butane called isobutane. Both of these structures fulfill the requirement that each carbon form four bonds and each hydrogen form one bond.

Compounds such as butane and isobutane that have the same molecular formula but differ in the way the atoms are connected are called **constitutional isomers**—their molecules have different constitutions. In fact, isobutane got its name because it is an *iso*mer of butane. The structural unit consisting of *a carbon bonded to a hydrogen and two* CH_3 *groups*, which occurs in isobutane, has come to be called "iso." Thus, the name *isobutane* tells you that the compound is a four-carbon alkane with an iso structural unit.

There are three alkanes with molecular formula C_5H_{12}. You have already learned how to name two of them. Pentane is the straight-chain alkane. Isopentane, as its name indicates, has an iso structural unit and five carbons. We cannot name the other branched-chain alkane without defining a name for a new structural unit. (For now, ignore the names written in blue.)

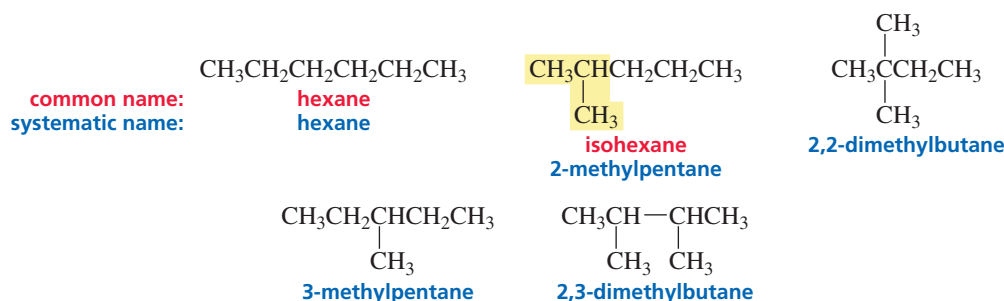
$CH_3CH_2CH_2CH_2CH_3$
pentane

$CH_3CH(CH_3)CH_2CH_3$
isopentane

$CH_3C(CH_3)_2CH_3$
2,2-dimethylpropane

There are five constitutional isomers with molecular formula C_6H_{14}. Again, we are able to name only two of them, unless we define new structural units.

	$CH_3CH_2CH_2CH_2CH_2CH_3$	$CH_3CH(CH_3)CH_2CH_2CH_3$	$CH_3C(CH_3)_2CH_2CH_3$
common name:	hexane	isohexane	
systematic name:	hexane	2-methylpentane	2,2-dimethylbutane

$CH_3CH_2CH(CH_3)CH_2CH_3$
3-methylpentane

$CH_3CH(CH_3)—CH(CH_3)CH_3$
2,3-dimethylbutane

The number of constitutional isomers increases rapidly as the number of carbons in an alkane increases. For example, there are 9 alkanes with molecular formula C_7H_{16}, 75 alkanes with molecular formula $C_{10}H_{22}$, and 4347 with molecular formula $C_{15}H_{32}$. To avoid having to memorize the names of thousands of structural units, chemists have devised rules for creating systematic names that describe the compound's structure. That way, only the rules have to be learned. Because the name describes the structure, these rules make it possible to deduce the structure of a compound from its name.

This method of nomenclature is called **systematic nomenclature.** It is also called **IUPAC nomenclature** because it was designed by a commission of the International Union of Pure and Applied Chemistry (abbreviated IUPAC and pronounced "eye-you-pack") in 1892.

The IUPAC rules have been continually revised by the commission since then. A name such as *isobutane*—a nonsystematic name—is called a **common name.** When both names are shown in this book, common names will be shown in red and systematic (IUPAC) names in blue. Before we can understand how a systematic name for an alkane is constructed, we must learn how to name alkyl substituents.

PROBLEM 1♦

a. How many hydrogens does an alkane with 17 carbons have?
b. How many carbons does an alkane with 74 hydrogens have?

PROBLEM 2

Draw the structures of octane and isooctane.

3.1 HOW ALKYL SUBSTITUENTS ARE NAMED

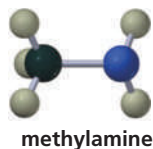
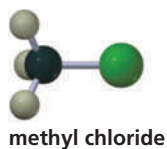
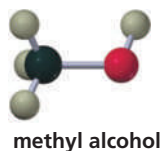
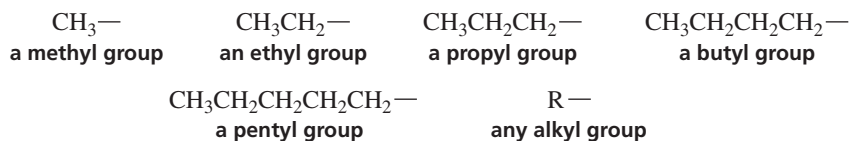
Removing a hydrogen from an alkane results in an **alkyl substituent** (or an alkyl group). Alkyl substituents are named by replacing the "ane" ending of the alkane with "yl." The letter "R" is used to indicate any alkyl group.

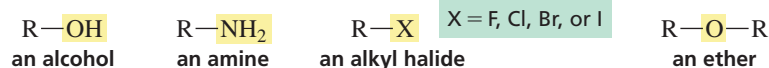
$CH_3—$	$CH_3CH_2—$	$CH_3CH_2CH_2—$	$CH_3CH_2CH_2CH_2—$
a methyl group	an ethyl group	a propyl group	a butyl group

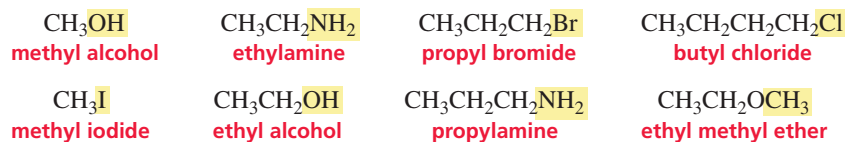
$CH_3CH_2CH_2CH_2CH_2—$	$R—$
a pentyl group	any alkyl group

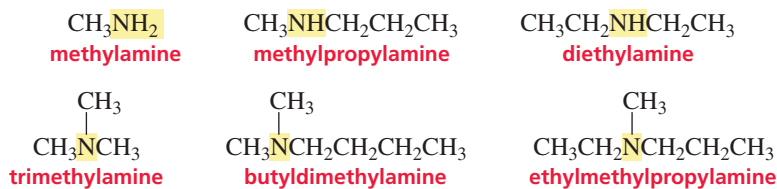
methyl alcohol

methyl chloride

methylamine

If a hydrogen in an alkane is replaced by an OH, the compound becomes an **alcohol;** if it is replaced by an NH_2, the compound becomes an **amine;** if it is replaced by a halogen, the compound becomes an **alkyl halide;** and if it is replaced by an OR, the compound becomes an **ether.**

an alcohol · an amine · an alkyl halide · an ether

The alkyl group name followed by the name of the class of the compound (alcohol, amine, etc.) yields the common name of the compound. The two alkyl groups in ethers are listed in alphabetical order. The following examples show how alkyl group names are used to build common names:

CH_3OH	$CH_3CH_2NH_2$	$CH_3CH_2CH_2Br$	$CH_3CH_2CH_2CH_2Cl$
methyl alcohol	ethylamine	propyl bromide	butyl chloride
CH_3I	CH_3CH_2OH	$CH_3CH_2CH_2NH_2$	$CH_3CH_2OCH_3$
methyl iodide	ethyl alcohol	propylamine	ethyl methyl ether

Notice that for most compounds there is a space between the name of the alkyl group and the name of the class of compound. For amines, however, the entire name is written as one word.

Amines can have one, two, or three of the hydrogens of NH_3 replaced by alkyl groups. The alkyl groups are listed in alphabetical order.

PROBLEM 3♦

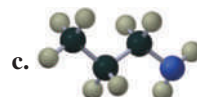
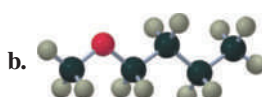
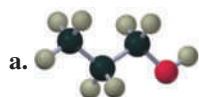
Name each of the following:

a.

b.

c.

Bad-Smelling Compounds

The citric acid in lemon juice decreases the fishy taste.

Amines are responsible for some of nature's unpleasant odors. Amines with relatively small alkyl groups have a fishy smell. For example, fermented shark, a traditional dish in Iceland, smells exactly like triethylamine. Fish is often served with lemon, because the citric acid in lemon protonates the amine, thereby converting it to non-volatile (odorless) acidic form.

$$CH_3CH_2-\ddot{N}(CH_2CH_3)_2 + HOOC-CH_2-C(OH)(COOH)-CH_2-COOH \rightleftharpoons CH_3CH_2-\overset{+}{N}H(CH_2CH_3)_2 + HOOC-CH_2-C(OH)(COO^-)-CH_2-COOH$$

triethylamine
bad smelling

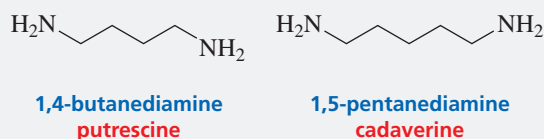
citric acid

protonated triethylamine
odorless

conjugate base of citric acid

The amines putrescine and cadaverine are poisonous compounds formed when amino acids are degraded in the body. Because these amines are excreted as quickly as possible, their odors may be detected in the urine and breath. Putrescine and cadaverine are also responsible for the odor of decaying flesh.

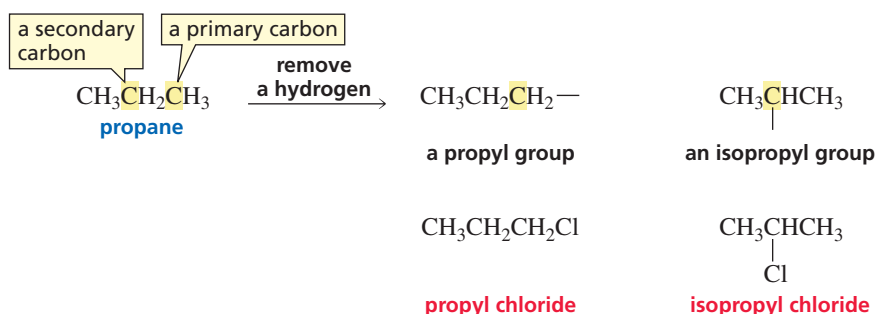
$H_2N(CH_2)_4NH_2$ — 1,4-butanediamine, putrescine

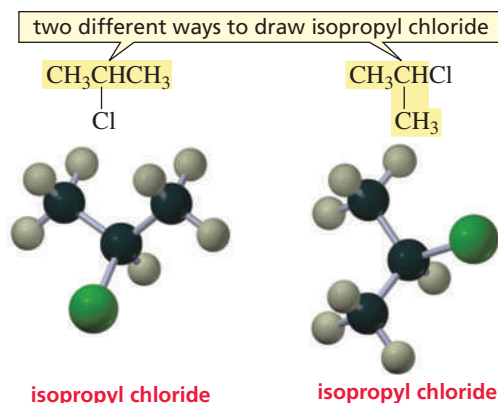
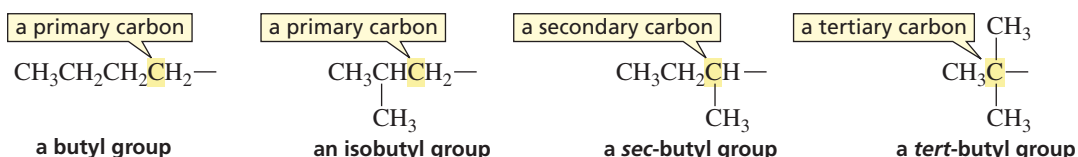
$H_2N(CH_2)_5NH_2$ — 1,5-pentanediamine, cadaverine

There are two alkyl groups—the propyl group and the isopropyl group—that have three carbons. A propyl group is obtained when a hydrogen is removed from *a primary carbon* of propane. A **primary carbon** is a carbon bonded to only one other carbon. An isopropyl group is obtained when a hydrogen is removed from the *secondary carbon* of propane. A **secondary carbon** is a carbon bonded to two other carbons. Notice that an isopropyl group, as its name indicates, has three carbon atoms arranged as an iso structural unit—that is, a carbon bonded to a hydrogen and to two CH_3 groups.

a secondary carbon; a primary carbon

$CH_3CH_2CH_3$ (propane) $\xrightarrow{\text{remove a hydrogen}}$ $CH_3CH_2CH_2-$ (a propyl group); $CH_3\underset{|}{C}HCH_3$ (an isopropyl group)

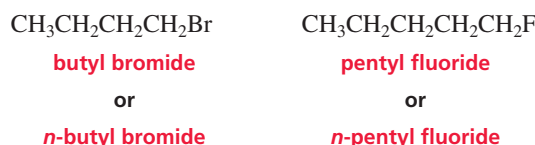
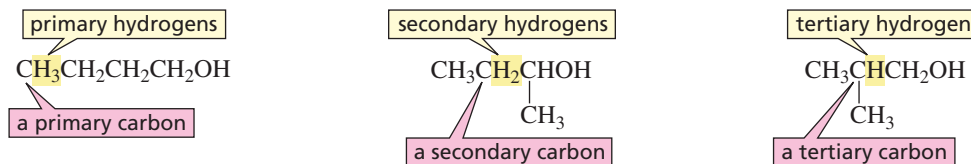
$CH_3CH_2CH_2Cl$ — propyl chloride

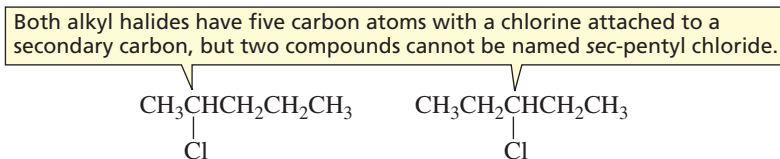
$CH_3CH(Cl)CH_3$ — isopropyl chloride

Molecular structures can be drawn in different ways. For example, isopropyl chloride is drawn below in two different ways. Both representations depict the same compound. Although the two-dimensional representations may appear at first to be different (the methyl groups are placed at opposite ends in one structure and at right angles in the other), the structures are identical because carbon is tetrahedral. The four groups bonded to the central carbon—a hydrogen, a chlorine, and two methyl groups—point to the corners of a tetrahedron (page 49). If you rotate the three-dimensional model on the right 90° in a clockwise direction, you should be able to see that the two models are the same.

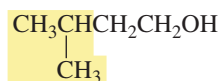
Build models of the two representations of isopropyl chloride to see that they represent the same compound.

There are four alkyl groups that have four carbons. Two of them, the butyl and isobutyl groups, have a hydrogen removed from a primary carbon. A *sec*-butyl group has a hydrogen removed from a secondary carbon (*sec*-, sometimes abbreviated *s*-, stands for secondary), and a *tert*-butyl group has a hydrogen removed from a tertiary carbon (*tert*-, often abbreviated *t*-, stands for tertiary). A **tertiary carbon** is a carbon that is bonded to three other carbons. Notice that the isobutyl group is the only one with an iso structural unit.

A primary carbon is bonded to one carbon, a secondary carbon is bonded to two carbons, and a tertiary carbon is bonded to three carbons.

The names of straight-chain alkyl groups often have the prefix "*n*" (for "normal") to emphasize that the carbons are in an unbranched chain. If a name does not have a prefix such as "*n*," "iso," "*sec*," or "*tert*," we assume that the carbons are in an unbranched chain.

$CH_3CH_2CH_2CH_2Br$ — butyl bromide or *n*-butyl bromide

$CH_3CH_2CH_2CH_2CH_2F$ — pentyl fluoride or *n*-pentyl fluoride

Like the carbons, the hydrogens in a molecule are also referred to as primary, secondary, and tertiary. **Primary hydrogens** are attached to a primary carbon, **secondary hydrogens** are attached to a secondary carbon, and **tertiary hydrogens** are attached to a tertiary carbon.

Primary hydrogens are attached to a primary carbon, secondary hydrogens to a secondary carbon, and tertiary hydrogens to a tertiary carbon.

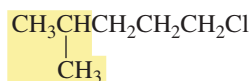
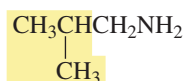
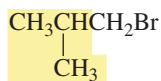
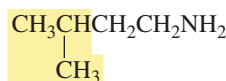
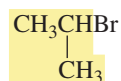
A chemical name must specify one compound only. The prefix "*sec*," therefore, can be used only for *sec*-butyl compounds. The name "*sec*-pentyl" cannot be used because pentane has two different secondary carbons. Thus, removing a hydrogen from a secondary carbon of pentane produces one of two different alkyl groups, depending on which hydrogen is removed. As a result, *sec*-pentyl chloride would specify two different alkyl chlorides, so it is *not* a correct name.

A name must specify one compound only.

Notice in the following structures that whenever the prefix “iso” is used, the iso structural unit is at one end of the molecule, and any group replacing a hydrogen is at the other end:

$CH_3CHCH_2CH_2OH$ with CH_3 on C-2
isopentyl alcohol

$CH_3CHCH_2CH_2CH_2Cl$ with CH_3 on C-2
isohexyl chloride

$CH_3CHCH_2NH_2$ with CH_3 on C-2
isobutylamine

CH_3CHCH_2Br with CH_3 on C-2
isobutyl bromide

$CH_3CHCH_2CH_2NH_2$ with CH_3 on C-2
isopentylamine

CH_3CHBr with CH_3 on C-2
isopropyl bromide

Alkyl group names are used so frequently that you need to learn them. Some of the most common alkyl group names are compiled in Table 3.2.

Table 3.2 Names of Some Common Alkyl Groups

methyl	$CH_3—$	isobutyl	$CH_3CHCH_2—$ | CH_3	pentyl	$CH_3CH_2CH_2CH_2CH_2—$
ethyl	$CH_3CH_2—$			isopentyl	$CH_3CHCH_2CH_2—$ | CH_3
propyl	$CH_3CH_2CH_2—$	*sec*-butyl	$CH_3CH_2CH—$ | CH_3		
isopropyl	$CH_3CH—$ | CH_3				
				hexyl	$CH_3CH_2CH_2CH_2CH_2CH_2—$
butyl	$CH_3CH_2CH_2CH_2—$	*tert*-butyl	CH_3 | $CH_3C—$ | CH_3	isohexyl	$CH_3CHCH_2CH_2CH_2—$ | CH_3

PROBLEM 4♦

Draw the structures and name the four constitutional isomers with molecular formula C_4H_9Br.

PROBLEM 5♦

Draw the structure for each of the following compounds:

a. isopropyl alcohol
b. isopentyl fluoride
c. *sec*-butyl iodide
d. *tert*-pentyl alcohol
e. *tert*-butylamine
f. *n*-octyl bromide

PROBLEM 6♦

Name the following compounds:

a. $CH_3OCH_2CH_3$
b. $CH_3NHCH_2CH_2CH_3$
c. $CH_3CH_2CHNH_2$ with CH_3 on the CH
d. $CH_3CH_2CH_2CH_2OH$
e. CH_3CHCH_2Br with CH_3 on the CH
f. CH_3CH_2CHCl with CH_3 on the CH

PROBLEM 7♦

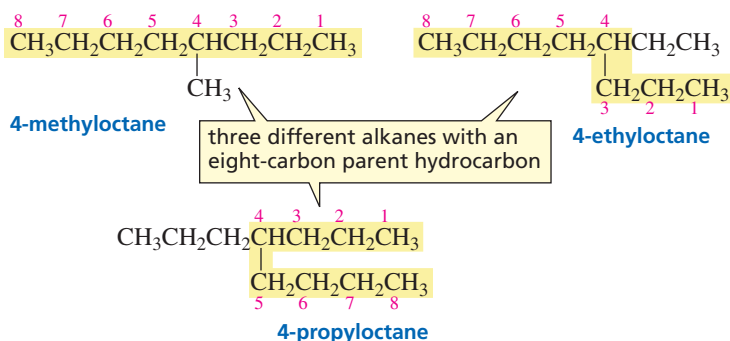
Draw the structure and give the systematic name of a compound with molecular formula C_5H_{12} that has

a. one tertiary carbon.
b. no secondary carbons.

3.2 THE NOMENCLATURE OF ALKANES

The systematic name of an alkane is obtained using the following rules:

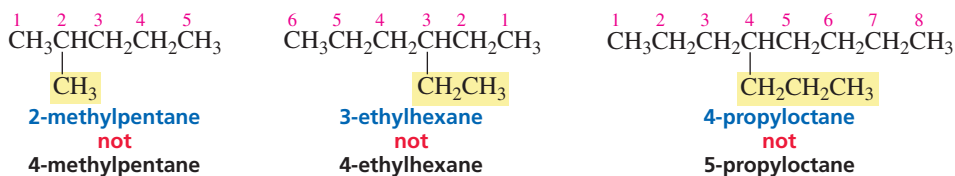
1. Determine the number of carbons in the longest continuous carbon chain. This chain is called the **parent hydrocarbon**. The name that indicates the number of carbons in the parent hydrocarbon becomes the alkane's "last name." For example, a parent hydrocarbon with eight carbons would be called *octane*. The longest continuous chain is not always in a straight line; sometimes you have to "turn a corner" to obtain the longest continuous chain.

First, determine the number of carbons in the longest continuous chain.

2. The name of any alkyl substituent that hangs off the parent hydrocarbon is placed in front of the name of the parent hydrocarbon, together with a number to designate the carbon to which the alkyl substituent is attached. The carbons in the parent hydrocarbon are numbered in the direction that gives the substituent as low a number as possible. The substituent's name and the name of the parent hydrocarbon are joined into one word, preceded by a hyphen that connects the substituent's number with its name.

Number the chain in the direction that gives the substituent as low a number as possible.

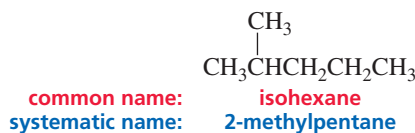
$CH_3\underset{|}{C}HCH_2CH_2CH_3$ with CH_3 on C-2 (numbered 1 2 3 4 5)
2-methylpentane not **4-methylpentane**

$CH_3CH_2CH_2\underset{|}{C}HCH_2CH_3$ with CH_2CH_3 on C-3 (numbered 6 5 4 3 2 1)
3-ethylhexane not **4-ethylhexane**

$CH_3CH_2CH_2\underset{|}{C}HCH_2CH_2CH_2CH_3$ with $CH_2CH_2CH_3$ on C-4 (numbered 1 2 3 4 5 6 7 8)
4-propyloctane not **5-propyloctane**

Only systematic names have numbers; common names *never* contain numbers.

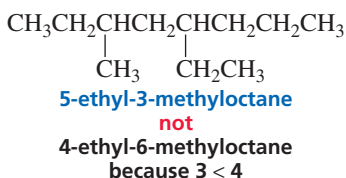
Numbers are used only for systematic names, never for common names.

$CH_3\underset{|}{C}HCH_2CH_2CH_3$ with CH_3 on C-2

common name: isohexane
systematic name: 2-methylpentane

3. If more than one substituent is attached to the parent hydrocarbon, the chain is numbered in the direction that will produce a name containing the lowest of the possible numbers. The substituents are listed in alphabetical order, with each substituent preceded by the appropriate number. In the following example, the correct name contains a 3 as its lowest number, whereas the incorrect name contains a 4 as its lowest number:

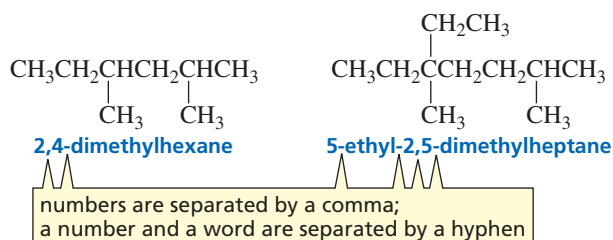
Substituents are listed in alphabetical order.

$CH_3CH_2\underset{|}{C}HCH_2\underset{|}{C}HCH_2CH_2CH_3$ with CH_3 and CH_2CH_3 substituents

5-ethyl-3-methyloctane
not
4-ethyl-6-methyloctane
because 3 < 4

If two or more substituents are the same, the prefixes "di," "tri," and "tetra" are used to indicate how many identical substituents the compound has. The numbers indicating the locations of the identical substituents are listed together, separated by commas. There are no spaces on either side of a comma. There must be as many numbers in a name as there are substituents. The prefixes "di," "tri," "tetra," "*sec*," and "*tert*" are ignored in alphabetizing substituents.

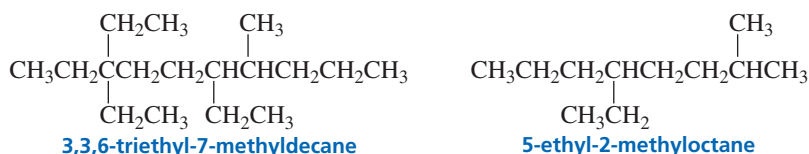
$CH_3CH_2CHCH_2CHCH_3$ with CH_3 on C2 and C4
2,4-dimethylhexane

$CH_3CH_2C(CH_2CH_3)(CH_3)CH_2CH_2CHCH_3$ with CH_3 on C2
5-ethyl-2,5-dimethylheptane

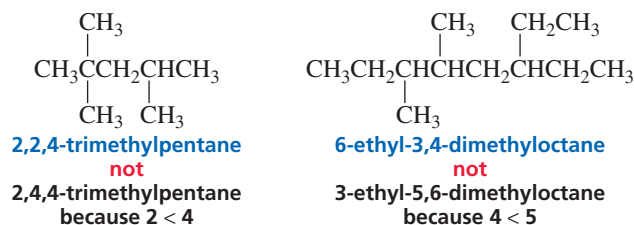
numbers are separated by a comma;
a number and a word are separated by a hyphen

A number and a word are separated by a hyphen;
numbers are separated by a comma.

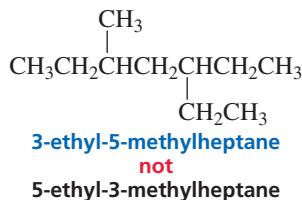
"di," "tri," "tetra," "*sec*," and "*tert*" are ignored in alphabetizing substituents.

$CH_3CH_2C(CH_2CH_3)_2CH_2CH_2CH(CH_2CH_3)CH(CH_3)CH_2CH_2CH_3$
3,3,6-triethyl-7-methyldecane

$CH_3CH_2CH_2CH(CH_2CH_3)CH_2CH_2CH(CH_3)CH_3$
5-ethyl-2-methyloctane

4. When numbering in either direction leads to the same lowest number for one of the substituents, the chain is numbered in the direction that gives the lowest possible number to one of the remaining substituents.

$CH_3C(CH_3)_2CH_2CH(CH_3)CH_3$
2,2,4-trimethylpentane
not
2,4,4-trimethylpentane
because 2 < 4

$CH_3CH_2CH(CH_3)CH(CH_3)CH_2CH(CH_2CH_3)CH_2CH_3$
6-ethyl-3,4-dimethyloctane
not
3-ethyl-5,6-dimethyloctane
because 4 < 5

5. If the same substituent numbers are obtained in both directions, the first group listed receives the lower number.

$CH_3CH_2CH(CH_3)CH_2CH(CH_2CH_3)CH_2CH_3$
3-ethyl-5-methylheptane
not
5-ethyl-3-methylheptane

Only if the same set of numbers is obtained in both directions does the first group listed get the lower number.

These rules will allow you to name thousands of alkanes, and eventually you will learn the additional rules necessary to name many other kinds of compounds. However, you must also learn common names because they are so entrenched in chemists' vocabularies that they are widely used in scientific conversation and are often found in the literature.

How Is the Octane Number of Gasoline Determined?

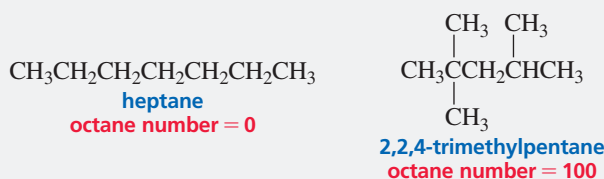
The gasoline engines used in most cars operate by creating a series of carefully timed, controlled explosions. In the engine cylinders, fuel is mixed with air, compressed, and then ignited by a spark. When the fuel used is too easily ignited, then the heat of compression can initiate combustion before the spark plug fires. A pinging or knocking may then be heard in the running engine.

As the quality of the fuel improves, the engine is less likely to knock. The quality of a fuel is indicated by its octane number. Straight-chain hydrocarbons have low octane numbers and make poor fuels. Heptane, for example, with an arbitrarily assigned octane number of 0, causes engines to knock badly. Branched-chain alkanes have more hydrogens bonded to primary carbons. These are the bonds that require the most energy to break and, therefore, make combustion more difficult to initiate, thereby reducing knocking. For example, 2,2,4-trimethylheptane does not cause knocking and has arbitrarily been assigned an octane number of 100.

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$$

heptane
octane number = 0

$$\begin{array}{c} CH_3 \quad CH_3 \\ | \qquad | \\ CH_3\overset{}{C}CH_2CHCH_3 \\ | \\ CH_3 \end{array}$$

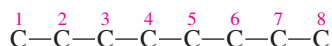
2,2,4-trimethylpentane
octane number = 100

The octane number of a gasoline is determined by comparing its knocking with the knocking of mixtures of heptane and 2,2,4-trimethylpentane. The octane number given to the gasoline corresponds to the percent of 2,2,4-trimethylpentane in the matching mixture. Thus, a gasoline with an octane rating of 91 has the same "knocking" property as a mixture of 91% 2,2,4-trimethylpentane and 9% heptane. The term *octane number* originated from the fact that 2,2,4-trimethylpentane contains eight carbons. Because slightly different methods are used to determine the octane number, gasoline in Canada and the United States will have an octane number that is 4 to 5 points less than the same gasoline in Europe and Australia.

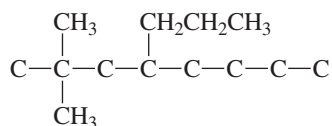
PROBLEM 8♦ Solved

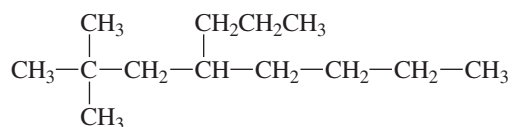
Draw the structure for each of the following compounds:

a. 2,2-dimethyl-4-propyloctane
b. 2,3-dimethylhexane
c. 2,4,5-trimethylheptane
d. 3,6-diethyl-3,6-dimethylnonane

Solution to 8a The parent (last) name is *octane*, so the longest continuous chain has eight carbons. Now draw the parent chain and number it.

$$\overset{1}{C}-\overset{2}{C}-\overset{3}{C}-\overset{4}{C}-\overset{5}{C}-\overset{6}{C}-\overset{7}{C}-\overset{8}{C}$$

Put the substituents (two methyl groups and a propyl group) on the appropriate carbons.

$$\begin{array}{c} \quad CH_3 \qquad CH_2CH_2CH_3 \\ C-\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}-C-\overset{|}{C}-C-C-C-C \end{array}$$

Add the appropriate number of hydrogens so each carbon is bonded to four atoms.

$$\begin{array}{c} \quad CH_3 \qquad\qquad CH_2CH_2CH_3 \\ CH_3-\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}-CH_2-\overset{|}{CH}-CH_2-CH_2-CH_2-CH_3 \end{array}$$

PROBLEM 9 Solved

a. Draw the 18 constitutional isomers with molecular formula C_8H_{18}.
b. Give each isomer its systematic name.
c. How many isomers have common names?
d. Which isomers contain an isopropyl group?
e. Which isomers contain a *sec*-butyl group?
f. Which isomers contain a *tert*-butyl group?

Solution to 9a Start with the isomer with an eight-carbon continuous chain. Then draw isomers with a seven-carbon continuous chain plus one methyl group. Next, draw isomers with a six-carbon continuous chain plus two methyl groups or one ethyl group. Then draw isomers with a five-carbon continuous chain plus three methyl groups or one methyl group and one ethyl group. Finally, draw a four-carbon continuous chain with four methyl groups. (Your answers to Problem 9b will tell you whether you have drawn duplicate structures, because if two structures have the same systematic name, they represent the same compound.)

PROBLEM 10♦

What is each compound's systematic name?

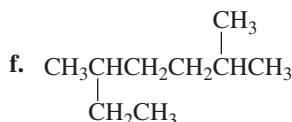
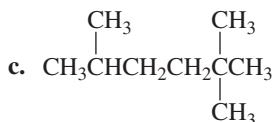
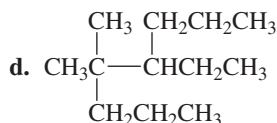
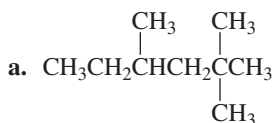
a. $CH_3CH_2CHCH_2CCH_3$ (with CH_3 on the third carbon; two CH_3 groups on the fifth carbon)

b. $CH_3CH_2C(CH_3)_3$

c. $CH_3CHCH_2CH_2CCH_3$ (with CH_3 on the second carbon; two CH_3 groups on the fifth carbon)

d. $CH_3C—CHCH_2CH_3$ (with CH_3 and $CH_2CH_2CH_3$ on the C; $CH_2CH_2CH_3$ on the CH)

e. $CH_3CH_2C(CH_2CH_3)_2CH_2CH_2CH_3$

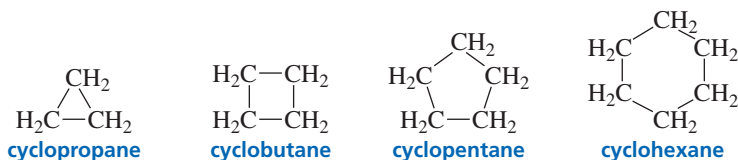
f. $CH_3CHCH_2CH_2CHCH_3$ (with CH_2CH_3 on the second carbon; CH_3 on the fifth carbon)

PROBLEM 11♦

Draw the structure and give the systematic name of a compound with molecular formula C_5H_{12} that has

a. only primary and secondary hydrogens.
b. only primary hydrogens.
c. one tertiary hydrogen.
d. two secondary hydrogens.

3.3 THE NOMENCLATURE OF CYCLOALKANES • SKELETAL STRUCTURES

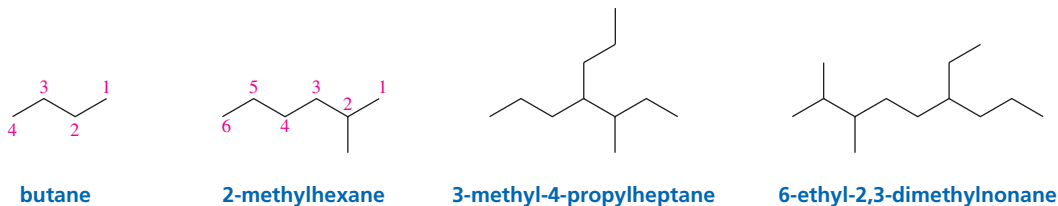
Cycloalkanes are alkanes with their carbon atoms arranged in a ring. Because of the ring, a cycloalkane has two fewer hydrogens than an acyclic (noncyclic) alkane with the same number of carbons. This means that the general molecular formula for a cycloalkane is C_nH_{2n}. Cycloalkanes are named by adding the prefix "cyclo" to the alkane name that signifies the number of carbons in the ring.

cyclopropane	cyclobutane	cyclopentane	cyclohexane
$(CH_2)_3$ ring: CH_2, $H_2C—CH_2$	$H_2C—CH_2$, $H_2C—CH_2$	CH_2, H_2C CH_2, $H_2C—CH_2$	CH_2, H_2C CH_2, H_2C CH_2, CH_2

Cycloalkanes are almost always written as **skeletal structures.** Skeletal structures show the carbon–carbon bonds as lines, but do not show the carbons or the hydrogens bonded to carbons. Each vertex in a skeletal structure represents a carbon, and each

carbon is understood to be bonded to the appropriate number of hydrogens to give the carbon four bonds.

cyclopropane cyclobutane cyclopentane cyclohexane

Acyclic molecules can also be represented by skeletal structures. In skeletal structures of acyclic molecules, the carbon chains are represented by zigzag lines. Again, each vertex represents a carbon, and carbons are assumed to be present where a line begins or ends.

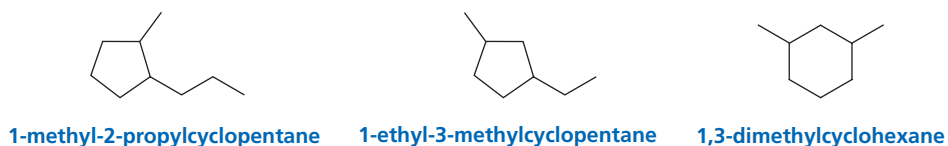
butane 2-methylhexane 3-methyl-4-propylheptane 6-ethyl-2,3-dimethylnonane

The rules for naming cycloalkanes resemble the rules for naming acyclic alkanes:

1. In a cycloalkane with an attached alkyl substituent, the ring is the parent hydrocarbon. *There is no need to number the position of a single substituent on a ring.*

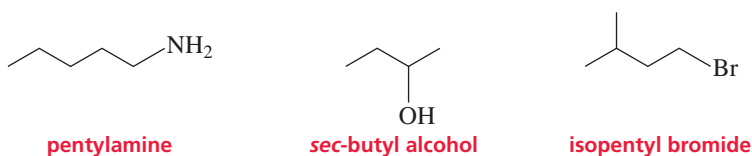
If there is only one substituent on a ring, do not give that substituent a number.

methylcyclopentane ethylcyclohexane

2. If the ring has two different substituents, they are listed in *alphabetical order* and the number-1 position is given to the substituent listed first.

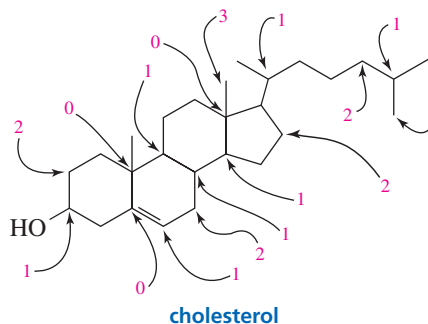
1-methyl-2-propylcyclopentane 1-ethyl-3-methylcyclopentane 1,3-dimethylcyclohexane

Skeletal structures can be drawn for compounds other than alkanes. Atoms other than carbon are shown, and hydrogens bonded to atoms other than carbon are also shown.

NH_2 OH Br

pentylamine *sec*-butyl alcohol isopentyl bromide

PROBLEM-SOLVING STRATEGY

Interpreting a Skeletal Structure

How many hydrogens are attached to each of the indicated carbons in cholesterol?

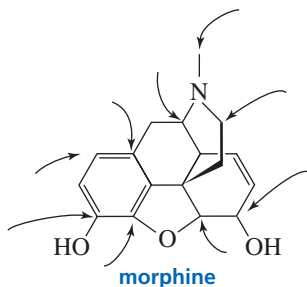
cholesterol

None of the carbons in the compound have a charge, so each needs to be bonded to four atoms. Thus, if the carbon has only one bond showing, it must be attached to three hydrogens that are not shown; if the carbon has two bonds showing, it must be attached to two hydrogens that are not shown, and so on. Check each of the answers (shown in red) to see that this is so.

Now use the strategy you have just learned to solve Problem 12.

PROBLEM 12

How many hydrogens are attached to each of the indicated carbons in morphine?

N
HO O OH

morphine

PROBLEM 13♦

Convert the following condensed structures into skeletal structures:

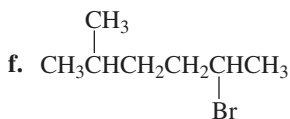
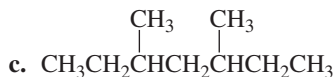
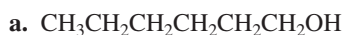
a. $CH_3CH_2CH_2CH_2CH_2CH_2OH$

b. $CH_3CH_2CH_2CH_2CH_2CH_3$

c. $CH_3CH_2\underset{|}{\overset{CH_3}{C}}HCH_2\overset{CH_3}{C}HCH_2CH_3$

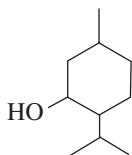
d. $CH_3CH_2CH_2CH_2OCH_3$

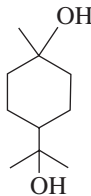
e. $CH_3CH_2NHCH_2CH_2CH_3$

f. $CH_3\overset{CH_3}{C}HCH_2CH_2\underset{Br}{C}HCH_3$

Condensed structures show atoms but show few, if any, bonds, whereas skeletal structures show bonds but show few, if any, atoms.

PROBLEM 14♦

The molecular formula for ethyl alcohol (CH_3CH_2OH) is C_2H_6O. What is the molecular formula for the following compounds?

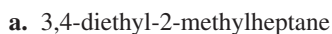
HO

menthol
found in peppermint oil

OH
OH

terpin hydrate
a common constituent of cough medicine

PROBLEM 15

Draw a condensed and a skeletal structure for the each of following:

a. 3,4-diethyl-2-methylheptane

b. 2,2,5-trimethylhexane

PROBLEM 16♦

What is each compound's systematic name?

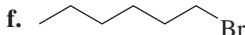
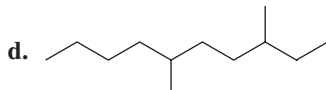
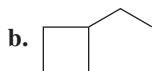
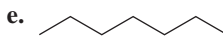
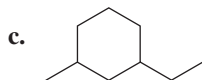
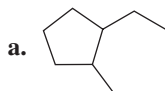
a.

b.

c.

d.

e.

f. Br

3.4 THE NOMENCLATURE OF ALKYL HALIDES

An **alkyl halide** is a compound in which a hydrogen of an alkane has been replaced by a halogen. The lone-pair electrons on the halogen are generally not shown unless they are needed to draw your attention to some chemical property of the atom.

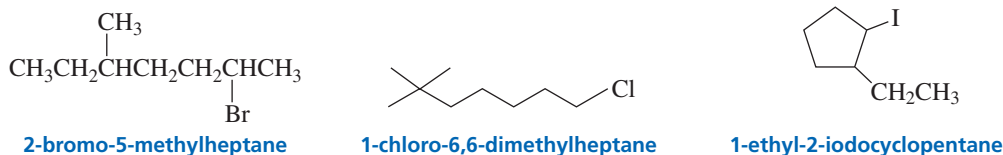
The common names of alkyl halides (red names) consist of the name of the alkyl group, followed by the name of the halogen—with the "ine" ending of the halogen name (fluorine, chlorine, bromine, and iodine) replaced by "ide" (fluoride, chloride, bromide, and iodide).

	CH_3Cl	CH_3CH_2F	CH_3CHI (with CH_3 on C-2)	CH_3CH_2CHBr (with CH_3 on the CHBr carbon)
common name:	methyl chloride	ethyl fluoride	isopropyl iodide	*sec*-butyl bromide
systematic name:	chloromethane	fluoroethane	2-iodopropane	2-bromobutane

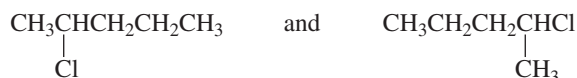
In the IUPAC system, alkyl halides are named as substituted alkanes (blue names). The prefixes for the halogens end with "o" (that is, fluoro, chloro, bromo, and iodo). Notice that although a compound can have more than one name, a name must specify only one compound.

$CH_3CH_2CH(CH_3)CH_2CH_2CH(Br)CH_3$
2-bromo-5-methylheptane

(skeletal structure) Cl
1-chloro-6,6-dimethylheptane

(cyclopentane with I and CH_2CH_3)
1-ethyl-2-iodocyclopentane

PROBLEM-SOLVING STRATEGY

Do the following structures represent the same compound or different compounds?

$CH_3CH(Cl)CH_2CH_2CH_3$ and $CH_3CH_2CH_2CH(Cl)CH_3$

The easiest way to answer this question is to determine the systematic names of the compounds. If they have the same systematic name, they are identical compounds; if they do not have the same systematic name, they are different compounds. Both structures are named 2-chloropentane; therefore, they represent the same compound.

$\overset{1}{C}H_3\overset{2}{C}H(Cl)\overset{3}{C}H_2\overset{4}{C}H_2\overset{5}{C}H_3$ and $\overset{5}{C}H_3\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}HCl(\overset{1}{C}H_3)$

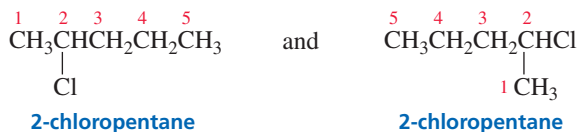
2-chloropentane and **2-chloropentane**

Now continue on to Problem 17.

CH_3F
methyl fluoride

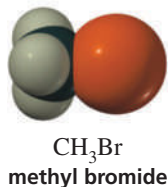
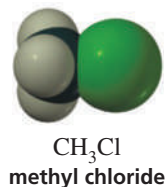
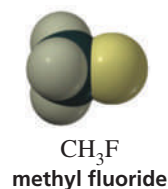
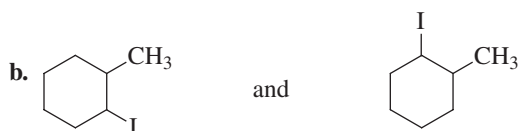
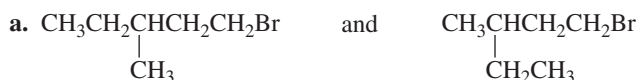
CH_3Cl
methyl chloride

CH_3Br
methyl bromide

CH_3I
methyl iodide

PROBLEM 17♦

Do the following structures represent the same compound or different compounds?

a. $CH_3CH_2CH(CH_3)CH_2CH_2Br$ and $CH_3CH(CH_2CH_3)CH_2CH_2Br$

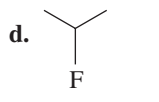
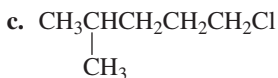
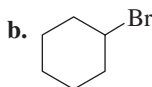
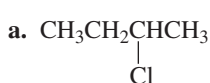
b. (cyclohexane with CH_3 and I on adjacent carbons) and (cyclohexane with I and CH_3 on adjacent carbons)

PROBLEM 18♦

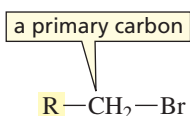
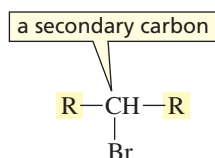
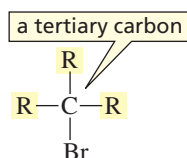
Give two names for each of the following alkyl halides:

a. $CH_3CH_2CHCH_3$ (with Cl on the CH carbon)

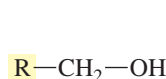
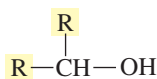
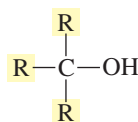
b. cyclohexane ring with Br

c. $CH_3CHCH_2CH_2CH_2Cl$ (with CH_3 on the CH carbon)

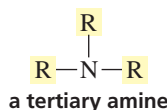
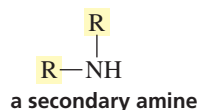
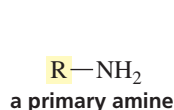
d. skeletal structure with F

3.5 THE CLASSIFICATION OF ALKYL HALIDES, ALCOHOLS, AND AMINES

Alkyl halides are classified as *primary, secondary*, or *tertiary*, depending on the carbon to which the halogen is attached. **Primary alkyl halides** have a halogen bonded to a primary carbon, **secondary alkyl halides** have a halogen bonded to a secondary carbon, and **tertiary alkyl halides** have a halogen bonded to a tertiary carbon (Section 3.1).

The number of alkyl groups attached to the carbon to which the halogen is bonded determines whether an alkyl halide is primary, secondary, or tertiary.

Alcohols are classified in the same way.

$R{-}CH_2{-}OH$ — a primary alcohol

$R{-}CH(R){-}OH$ — a secondary alcohol

$R{-}C(R)(R){-}OH$ — a tertiary alcohol

The number of alkyl groups attached to the carbon to which the OH group is bonded determines whether an alcohol is primary, secondary, or tertiary.

There are also *primary, secondary*, or *tertiary amines*; but in the case of amines, the terms have different meanings. The classification refers to how many alkyl groups are bonded to the nitrogen. **Primary amines** have one alkyl group bonded to the nitrogen, **secondary amines** have two, and **tertiary amines** have three. The common name of an amine consists of the names of all the alkyl groups bonded to the nitrogen, in alphabetical order, followed by "amine."

The number of alkyl groups attached to the nitrogen determines whether an amine is primary, secondary, or tertiary.

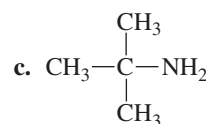
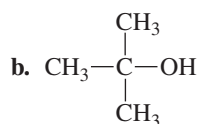
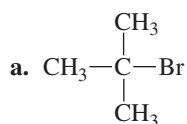
Nitrosamines and Cancer

A 1962 outbreak of food poisoning in sheep in Norway was traced to their ingestion of nitrite-treated fish meal. This incident immediately raised concerns about human consumption of nitrite-treated foods, because sodium nitrite ($NaNO_2$), a commonly used food preservative, can react with naturally occurring secondary amines that are present in food, to produce nitrosamines ($R_2NN{=}O$), which are known to be carcinogenic. Smoked fish, cured meats, and beer all contain nitrosamines. Nitrosamines are also found in cheese because some cheeses are preserved with sodium nitrite and cheese is rich in secondary amines. When consumer groups in the United States asked the Food and Drug Administration to ban the use of sodium nitrite as a preservative, the request was vigorously opposed by the meat-packing industry.

Despite extensive investigations, it has not yet been determined whether the small amounts of nitrosamines present in our food pose a hazard to our health. Until this question is answered, it will be hard to avoid sodium nitrite in our diet. Meanwhile, it is worrisome to note that Japan has both one of the highest gastric cancer rates and the highest average ingestion of sodium nitrite. Some good news, however, is that the concentration of nitrosamines present in bacon has been considerably reduced in recent years by the addition of ascorbic acid—a nitrosamine inhibitor—to the curing mixture. Also, improvements in the malting process have reduced the level of nitrosamines in beer. Dietary sodium nitrite does have a redeeming feature: there is some evidence that it protects against botulism, a type of severe food poisoning.

PROBLEM 19♦

Are the following compounds primary, secondary, or tertiary?

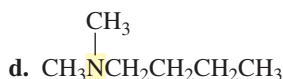
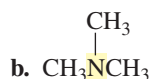
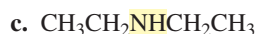
a. $CH_3-C(CH_3)_2-Br$ **b.** $CH_3-C(CH_3)_2-OH$ **c.** $CH_3-C(CH_3)_2-NH_2$

PROBLEM 20♦

Name the following amines and tell whether they are primary, secondary, or tertiary:

a. $CH_3NHCH_2CH_2CH_3$

b. $CH_3N(CH_3)CH_3$

c. $CH_3CH_2NHCH_2CH_3$

d. $CH_3N(CH_3)CH_2CH_2CH_2CH_3$

PROBLEM 21

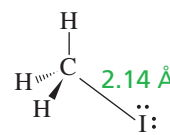
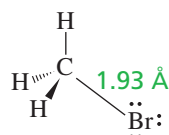
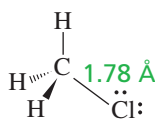
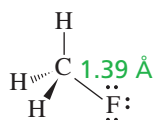
Draw the structures and provide systematic names for parts **a**, **b**, and **c** by substituting a chlorine for a hydrogen of methylcyclohexane:

a. a primary alkyl halide **b.** a tertiary alkyl halide **c.** three secondary alkyl halides

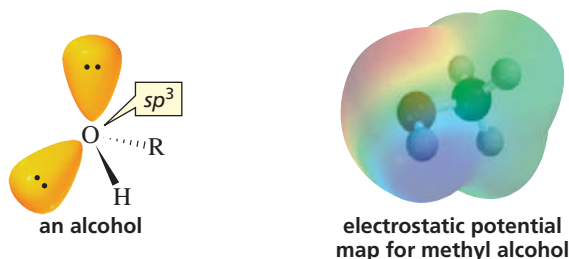
3.6 THE STRUCTURES OF ALKYL HALIDES, ALCOHOLS, ETHERS, AND AMINES

The families of compounds we have been looking at in this chapter have structural resemblances to the simpler compounds introduced in Chapter 1. Let's begin by looking at alkyl halides and their resemblance to alkanes. Both have the same geometry; the only difference is that a C—X bond of an alkyl halide (where X denotes a halogen) has replaced a C—H bond of an alkane (Section 1.7).

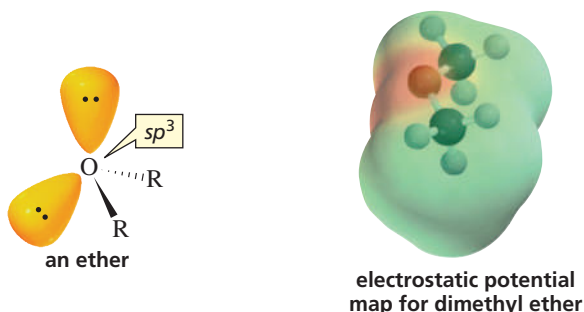
The C—X bond of an alkyl halide is formed from the overlap of an sp^3 orbital of carbon with an sp^3 orbital of the halogen. Fluorine uses a $2sp^3$ orbital to overlap with a $2sp^3$ orbital of carbon, chlorine uses a $3sp^3$ orbital, bromine a $4sp^3$ orbital, and iodine a $5sp^3$ orbital. Thus, the C—X bond becomes longer and weaker as the size of the halogen increases because the electron density of the orbital decreases with increasing volume. Notice that this is the same trend shown by the H—X bond of hydrogen halides in Table 1.6 on page 60.

CH_3F: C—F 1.39 Å CH_3Cl: C—Cl 1.78 Å CH_3Br: C—Br 1.93 Å CH_3I: C—I 2.14 Å

Now let's consider the geometry of the oxygen in an alcohol; it is the same as the geometry of the oxygen in water (Section 1.12). In fact, an alcohol molecule can be thought of structurally as a water molecule with an alkyl group in place of one of the hydrogens. The oxygen in an alcohol is sp^3 hybridized, as it is in water. Of the four sp^3 orbitals of oxygen, one overlaps an sp^3 orbital of a carbon, one overlaps the *s* orbital of a hydrogen, and the other two each contain a lone pair.

an alcohol

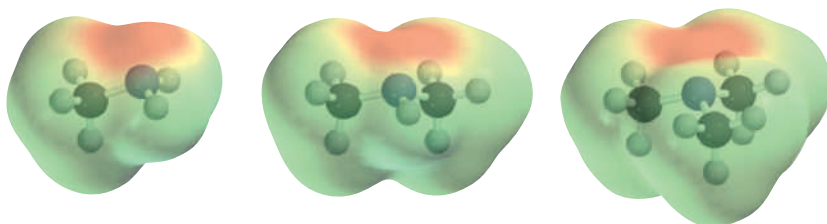
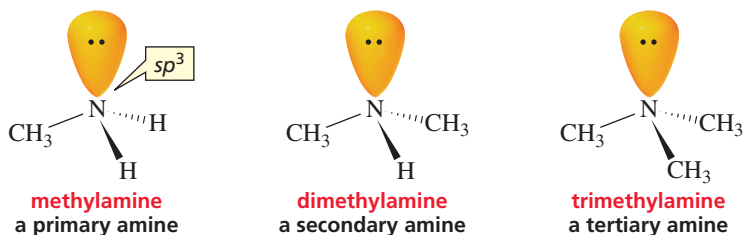
electrostatic potential map for methyl alcohol

The oxygen in an ether also has the same geometry as the oxygen in water. An ether molecule can be thought of structurally as a water molecule with alkyl groups in place of both hydrogens.

an ether

electrostatic potential map for dimethyl ether

The nitrogen in an amine has the same geometry as the nitrogen in ammonia (Section 1.11). The nitrogen is sp^3 hybridized as in ammonia, with one, two, or three of the hydrogens replaced by alkyl groups. Remember that the number of hydrogens replaced by alkyl groups determines whether the amine is primary, secondary, or tertiary (Section 3.5).

methylamine a primary amine

dimethylamine a secondary amine

trimethylamine a tertiary amine

PROBLEM 22♦

Predict the approximate size of the following bond angles. (*Hint:* See Sections 1.11 and 1.12.)

a. the C—O—C bond angle in an ether
b. the C—N—C bond angle in a secondary amine
c. the C—O—H bond angle in an alcohol

3.7 NONCOVALENT INTERACTIONS

Now we will look at noncovalent interactions—interactions that are weaker than covalent bonds—that can exist between molecules and see how these interactions affect the physical properties of organic compounds. The noncovalent interactions we will look at are van der Waals forces, dipole–dipole interactions, and hydrogen bonding.

Boiling Points

The **boiling point (bp)** of a compound is the temperature at which the liquid form becomes a gas (vaporizes). In order for a compound to vaporize, the forces that hold the individual molecules close to each other in the liquid must be overcome. Thus, the boiling point of a compound depends on the strength of the attractive forces between the individual molecules. If the molecules are held together by strong forces, a lot of energy will be needed to pull the molecules away from each other and the compound will have a high boiling point. On the other hand, if the molecules are held together by weak forces, only a small amount of energy will be needed to pull the molecules away from each other and the compound will have a low boiling point.

Van Der Waals Forces

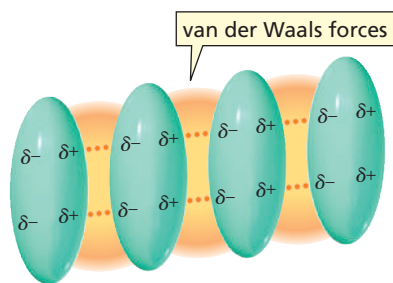
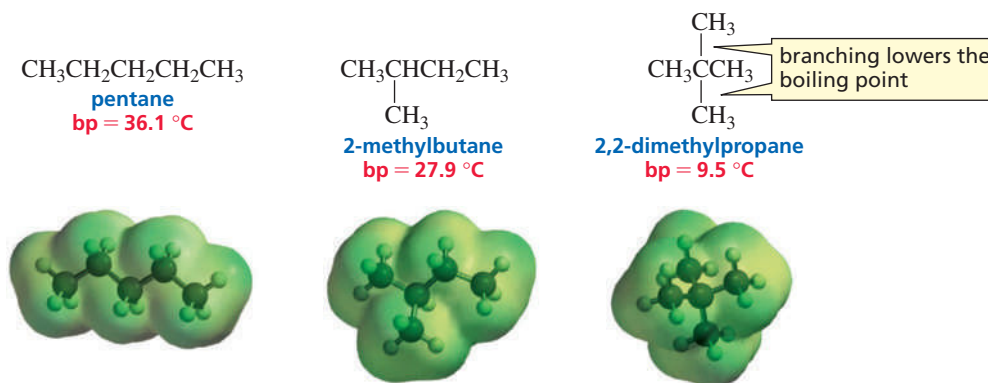
Alkanes contain only carbons and hydrogens. Because the electronegativities of carbon and hydrogen are similar, the bonds in alkanes are nonpolar—there are no significant partial charges on any of the atoms. Alkanes, therefore, are neutral, nonpolar molecules, so the attractive forces between them are relatively weak. The nonpolar nature of alkanes gives them their oily feel.

▲ **Figure 3.1**
Van der Waals forces, the weakest of all the attractive forces, are induced-dipole–induced-dipole interactions.

However, it is only the average charge distribution over the alkane molecule that is neutral. Electrons move continuously, and at any instant the electron density on one side of a molecule can be slightly greater than that on the other side, causing the molecule to have a temporary dipole. Recall that molecule with a dipole has a negative end and a positive end (Section 1.3).

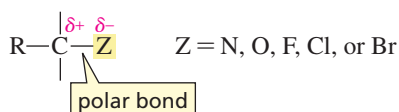
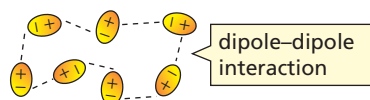
A temporary dipole in one molecule can induce a temporary dipole in a nearby molecule. As a result, the (temporarily) negative side of one molecule ends up adjacent to the (temporarily) positive side of another, as shown in Figure 3.1. Because the dipoles in the molecules are induced, the interactions between the molecules are called **induced-dipole–induced-dipole interactions.** The molecules of an alkane are held together by these induced-dipole–induced-dipole interactions, which are known as **van der Waals forces.** Van der Waals forces are the weakest of all the attractive forces.

The magnitude of the van der Waals forces that hold alkane molecules together depends on the area of contact between the molecules. The greater the area of contact, the stronger the van der Waals forces and the greater the amount of energy needed to overcome them. If you look at the boiling points of the alkanes listed in Table 3.1, you will see that they increase as their molecular weight increases, because each additional methylene (CH_2) group increases the area of contact between the molecules. The four smallest alkanes have boiling points below room temperature, so they exist as gases at room temperature.

Branching lowers a compound's boiling point by reducing the area of contact. If you think of *unbranched* pentane as a cigar and *branched* 2,2-dimethylpropane as a tennis ball, you can see that branching decreases the area of contact between molecules—that is, two cigars make contact over a greater surface area than do two tennis balls. Thus, if two alkanes have the same molecular weight, the more highly branched alkane will have a lower boiling point.

PROBLEM 23♦

What is the smallest straight-chain alkane that is a liquid at room temperature (which is about 25 °C)?

Dipole–Dipole Interactions

The boiling points of a series of ethers, alkyl halides, alcohols, or amines also increase with increasing molecular weight because of the increase in van der Waals forces. The boiling points of these compounds, however, are also affected by the polar C—Z bond. Recall that the C—Z bond is polar because nitrogen, oxygen, and the halogens are more electronegative than the carbon to which they are attached (Section 1.3).

Molecules with polar bonds are attracted to one another because they can align themselves in such a way that the positive end of one molecule is adjacent to the negative end of another molecule. These electrostatic attractive forces, called **dipole–dipole interactions,** are stronger than van der Waals forces, but not as strong as ionic or covalent bonds.

Ethers generally have higher boiling points than alkanes of comparable molecular weight because *both* van der Waals forces *and* dipole–dipole interactions must be overcome for an ether to boil (Table 3.3).

cyclopentane
bp = 49.3 °C

O
tetrahydrofuran
bp = 65 °C

The boiling point of a compound depends on the strength of the attractions between the individual molecules.

Table 3.3 Comparative Boiling Points (°C)

Alkanes	Ethers	Alcohols	Amines
$CH_3CH_2CH_3$	CH_3OCH_3	CH_3CH_2OH	$CH_3CH_2NH_2$
–42.1	–23.7	78	16.6
$CH_3CH_2CH_2CH_3$	$CH_3OCH_2CH_3$	$CH_3CH_2CH_2OH$	$CH_3CH_2CH_2NH_2$
–0.5	10.8	97.4	47.8

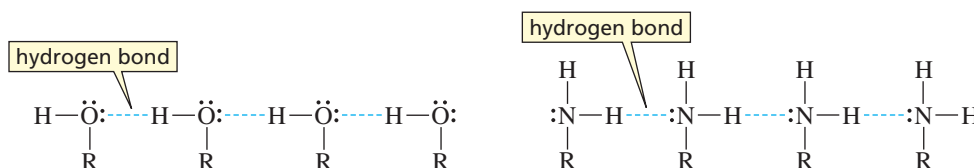
For an alkyl halide to boil, both van der Waals forces and dipole–dipole interactions must be overcome. As the halogen atom increases in size, the size of its electron cloud increases, and the larger the electron cloud, the stronger are the van der Waals forces. Therefore, an alkyl fluoride has a lower boiling point than an alkyl chloride with the same alkyl group. Similarly, alkyl chlorides have lower boiling points than analogous alkyl bromides, which have lower boiling points than analogous alkyl iodides (Table 3.4).

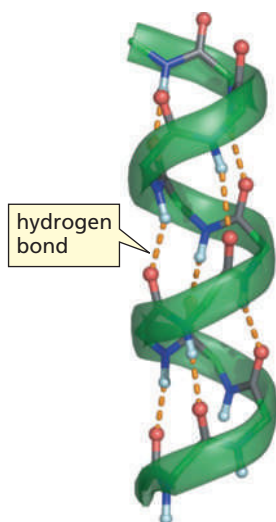
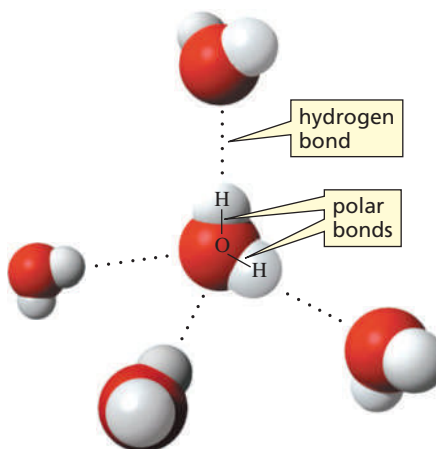
Table 3.4 Comparative Boiling Points of Alkanes and Alkyl Halides (°C)

—Y	H	F	Cl	Br	I
CH_3—Y	–161.7	–78.4	–24.2	3.6	42.4
CH_3CH_2—Y	–88.6	–37.7	12.3	38.4	72.3
$CH_3CH_2CH_2$—Y	–42.1	–2.5	46.6	71.0	102.5
$CH_3CH_2CH_2CH_2$—Y	–0.5	32.5	78.4	101.6	130.5
$CH_3CH_2CH_2CH_2CH_2$—Y	36.1	62.8	107.8	129.6	157.0

Hydrogen Bonds

Alcohols have much higher boiling points than ethers with similar molecular weights (Table 3.3) because, in addition to van der Waals forces and the dipole–dipole interactions of the polar C—O bond, alcohols can form **hydrogen bonds.** A hydrogen bond is a special kind of dipole–dipole interaction that occurs between a hydrogen that is attached to an oxygen, nitrogen, or fluorine and a lone pair of an oxygen, nitrogen, or fluorine in another molecule.

Hydrogen bonds are stronger than other dipole–dipole interactions, which are stronger than van der Waals forces.

A hydrogen bond is stronger than other dipole–dipole interactions. The extra energy required to break these hydrogen bonds is why alcohols have much higher boiling points than ethers with similar molecular weights.

The boiling point of water illustrates the dramatic effect that hydrogen bonding has on boiling points. Water has a molecular weight of 18 and a boiling point of 100 °C. The alkane nearest in size is methane, with a molecular weight of 16 and a boiling point of −167.7 °C.

▲ **Figure 3.2**
Hydrogen bonds hold a segment of a protein chain in a helical structure. Notice that each hydrogen bond forms between a lone pair on oxygen (red) and a hydrogen (white) that is attached to a nitrogen (blue).

Primary and secondary amines also form hydrogen bonds, so they have higher boiling points than ethers with similar molecular weights. Nitrogen is not as electronegative

as oxygen, however, so the hydrogen bonds between amine molecules are weaker than those between alcohol molecules. An amine, therefore, has a lower boiling point than an alcohol with a similar molecular weight (Table 3.3).

Hydrogen bonds play a crucial role in biology, including holding protein chains in the correct three-dimensional shape (Figure 3.2) and making it possible for DNA to copy all its hereditary information (Figure 3.3). These topics are discussed in detail in Chapter 20.

▲ Figure 3.3
DNA has two strands that run in opposite directions. The phosphates (P) and the sugars (five-membered rings) are on the outside, and the bases (A, G, T, and C) are on the inside. The two strands are held together by hydrogen bonding between the bases. A always pairs with T (using two hydrogen bonds), and G always pairs with C (using three hydrogen bonds). The structures of the bases that form the hydrogen bonds are shown on page 655.

PROBLEM 24♦

a. Which is longer, an O — H hydrogen bond or an O — H covalent bond?
b. Which is stronger?

PROBLEM-SOLVING STRATEGY

Predicting Hydrogen Bonding

a. Which of the following compounds will form hydrogen bonds between its molecules?
1. $CH_3CH_2CH_2OH$ **2.** $CH_3CH_2CH_2F$ **3.** $CH_3OCH_2CH_3$

b. Which of these compounds will form hydrogen bonds with a solvent such as ethanol?

To solve this type of question, start by defining the kind of compound that will do what is being asked.

a. A hydrogen bond forms when a hydrogen attached to an O, N, or F of one molecule interacts with a lone pair on an O, N, or F of another molecule. Therefore, a compound that will form hydrogen bonds with itself must have a hydrogen attached to an O, N, or F. Only compound **1** will be able to form hydrogen bonds with itself.

b. Ethanol has an H attached to an O, so it will be able to form hydrogen bonds with a compound that has a lone pair on an O, N, or F. All three compounds will be able to form hydrogen bonds with ethanol.

Now use the strategy you have just learned to solve Problem 25.

PROBLEM 25♦

a. Which of the following compounds will form hydrogen bonds between its molecules?

1. $CH_3CH_2OCH_2CH_2OH$	**3.** $CH_3CH_2CH_2CH_2Br$	**5.** $CH_3CH_2CH_2COOH$
2. $CH_3CH_2N(CH_3)_2$	**4.** $CH_3CH_2CH_2NHCH_3$	**6.** $CH_3CH_2CH_2CH_2F$

b. Which of the preceding compounds will form hydrogen bonds with a solvent such as ethanol?

PROBLEM 26♦

List the following compounds from highest boiling to lowest boiling:

OH HO OH OH OH OH NH_2

PROBLEM 27

List the compounds in each set from highest boiling to lowest boiling:

a. Br Br Br

b.

c. OH Cl OH

Drugs Bind to Their Receptors

Many drugs exert their physiological effects by binding to specific sites, called *receptors*, on the surface of certain cells (Section 6.18). A drug binds to a receptor using the same kinds of bonding interactions—van der Waals interactions, dipole–dipole interactions, hydrogen bonding—that molecules use to bind to each other.

The most important factor in the interaction between a drug and its receptor is a snug fit. Therefore, drugs with similar shapes and properties, which causes them to bind to the same receptor, have similar physiological effects. For example, each of the compounds shown here has a nonpolar, planar, six-membered ring and substituents with similar polarities. They all have anti-inflammatory activity and are known as NSAIDs (nonsteroidal anti-inflammatory drugs).

Salicylic acid has been used for the relief of fever and arthritic pain since 500 B.C. In 1897, acetylsalicylic acid (known by brand names such as Bayer Aspirin, Bufferin, Anacin, Ecotrin, and Ascriptin) was found to be a more potent anti-inflammatory agent and less irritating to the stomach; it became commercially available in 1899.

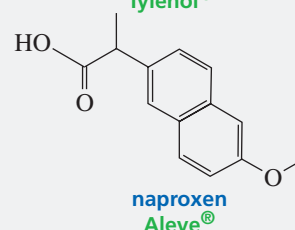
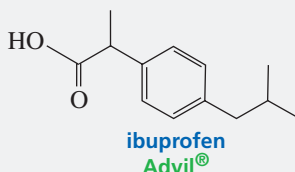
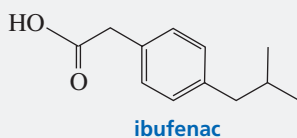
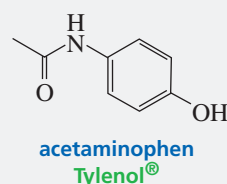
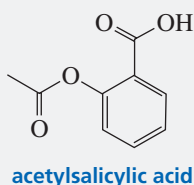
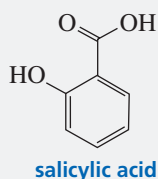
salicylic acid

acetylsalicylic acid

acetaminophen
Tylenol®

ibufenac

ibuprofen
Advil®

naproxen
Aleve®

Changing the substituents and their relative positions on the ring produced acetaminophen (Tylenol), which was introduced in 1955. It became a widely used drug because it causes no gastric irritation. However, its effective dose is not far from its toxic dose. Subsequently, ibufenac emerged; adding a methyl group to ibufenac produced ibuprofen (Advil), which is a much safer drug. Naproxen (Aleve), which has twice the potency of ibuprofen, was introduced in 1976.

Melting Points

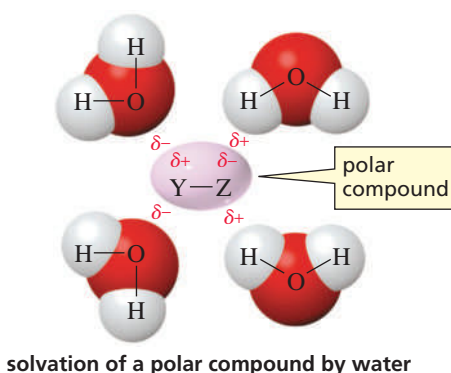
The **melting point (mp)** of a compound is the temperature at which its solid form is converted into a liquid. The melting points of the alkanes listed in Table 3.1 show that they increase (with a few exceptions) as the molecular weight increases. The increase in melting point is less regular than the increase in boiling point because, in addition to the intermolecular attractions we just considered, the melting point is influenced by the **packing** (that is, the arrangement, including the closeness and compactness, of the molecules) in the crystal lattice. The tighter the fit, the more energy is required to break the lattice and melt the compound.

3.8 FACTORS THAT AFFECT THE SOLUBILITY OF ORGANIC COMPOUNDS

The general rule that governs **solubility** is "like dissolves like." In other words,

> *Polar compounds dissolve in polar solvents;*
> *nonpolar compounds dissolve in nonpolar solvents.*

"Polar dissolves polar" because a polar solvent, such as water, has partial charges that can interact with the partial charges on a polar compound. The negative poles of the solvent molecules surround the positive pole of the polar compound, and the positive poles of the solvent molecules surround the negative pole of the polar compound. The clustering of the solvent molecules around the polar molecules separates them from each other, which is what makes them dissolve. The interaction between solvent molecules and solute molecules (molecules dissolved in a solvent) is called **solvation.**

solvation of a polar compound by water

"Like dissolves like."

Because nonpolar compounds have no charge, polar solvents are not attracted to them. In order for a nonpolar molecule to dissolve in a polar solvent such as water, the nonpolar molecule would have to push the water molecules apart, disrupting their hydrogen bonding. Hydrogen bonding, however, is strong enough to exclude the nonpolar compound. On the other hand, nonpolar solutes dissolve in nonpolar solvents because the van der Waals forces between solvent molecules and solute molecules are about the same as those between solvent molecules and those between solute molecules.

Smoke billows from a controlled burn of spilled oil off the Louisiana coast in the Gulf of Mexico.

Alkanes

Alkanes are nonpolar, so they are soluble in nonpolar solvents and insoluble in polar solvents such as water. The densities of alkanes increase with increasing molecular weight (Table 3.1), but even a 30-carbon alkane is less dense than water $(d^{20°} = 1.00 \text{ g/mL})$. Therefore, a mixture of an alkane and water will separate into two distinct layers, with the less dense alkane floating on top. The Alaskan oil spill in 1989, the Gulf War oil spill in 1991, and the oil spill in the Gulf of Mexico in 2010 are large-scale examples of this phenomenon because crude oil is primarily a mixture of alkanes.

Alcohols

Is an alcohol nonpolar because its alkyl group, or is it polar because of its OH group? It depends on the size of the alkyl group. As the alkyl group increases in size, becoming a more significant fraction of the entire alcohol molecule, the compound becomes less and less soluble in water. In other words, the molecule becomes more and more like an alkane. Groups with four carbons tend to straddle the dividing line at room temperature, so alcohols with fewer than four carbons are soluble in water, but alcohols with more than four carbons are insoluble in water. Thus, an OH group can drag about three or four carbons into solution in water.

The four-carbon dividing line is only an approximate guide because the solubility of an alcohol also depends on the structure of the alkyl group. Alcohols with branched alkyl groups are more soluble in water than alcohols with unbranched alkyl groups with the same number of carbons, because branching minimizes the contact surface of the nonpolar portion of the molecule. Thus, *tert*-butyl alcohol is more soluble than *n*-butyl alcohol in water.

Ethers

The oxygen of an ether, like the oxygen of an alcohol, can drag only about three carbons into solution in water (Table 3.5). The photo on page 88 shows that diethyl ether—an ether with four carbons—is not fully soluble in water.

Table 3.5 Solubilities of Ethers in Water

2 Cs	CH_3OCH_3	soluble
3 Cs	$CH_3OCH_2CH_3$	soluble
4 Cs	$CH_3CH_2OCH_2CH_3$	slightly soluble (10 g/100 g H_2O)
5 Cs	$CH_3CH_2OCH_2CH_2CH_3$	minimally soluble (1.0 g/100 g H_2O)
6 Cs	$CH_3CH_2CH_2OCH_2CH_2CH_3$	insoluble (0.25 g/100 g H_2O)

Amines

Low-molecular-weight amines are soluble in water because amines can form hydrogen bonds with water. Primary, secondary, and tertiary amines have a lone pair they use to form a hydrogen bond. Primary amines are more soluble than secondary amines with the same number of carbons, because primary amines have two hydrogens that can engage in hydrogen bonding with water. Tertiary amines do not have hydrogens to donate for hydrogen bonds, so they are less soluble in water than are secondary amines with the same number of carbons.

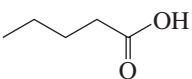
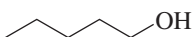
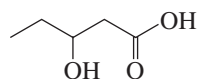
Alkyl Halides

Alkyl halides have some polar character, but only alkyl fluorides have an atom that can form a hydrogen bond with water. Alkyl fluorides, therefore, are the most water soluble of the alkyl halides. The other alkyl halides are less soluble in water than ethers or alcohols with the same number of carbons (Table 3.6).

Table 3.6 Solubilities of Alkyl Halides in Water

CH_3F very soluble	CH_3Cl soluble	CH_3Br slightly soluble	CH_3I slightly soluble
CH_3CH_2F soluble	CH_3CH_2Cl slightly soluble	CH_3CH_2Br slightly soluble	CH_3CH_2I slightly soluble
$CH_3CH_2CH_2F$ slightly soluble	$CH_3CH_2CH_2Cl$ slightly soluble	$CH_3CH_2CH_2Br$ slightly soluble	$CH_3CH_2CH_2I$ slightly soluble
$CH_3CH_2CH_2CH_2F$ insoluble	$CH_3CH_2CH_2CH_2Cl$ insoluble	$CH_3CH_2CH_2CH_2Br$ insoluble	$CH_3CH_2CH_2CH_2I$ insoluble

PROBLEM 28♦

Rank the following compounds in each set from most soluble to least soluble in water:

a. OH O   OH   OH OH O

b. $CH_3CH_2CH_2OH$ $CH_3CH_2CH_2CH_2Cl$ $CH_3CH_2CH_2CH_2OH$ $HOCH_2CH_2CH_2OH$

PROBLEM 29♦

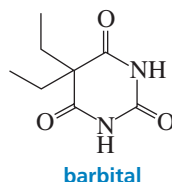
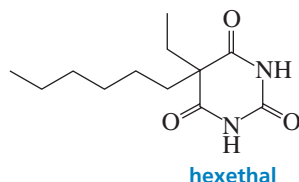
In which solvent would cyclohexane have the lowest solubility: 1-pentanol, diethyl ether, ethanol, or hexane?

Cell Membranes

Cell membranes demonstrate how nonpolar molecules are attracted to other nonpolar molecules, whereas polar molecules are attracted to other polar molecules. All cells are enclosed by a membrane that prevents the aqueous (polar) contents of the cell from pouring out into the aqueous fluid that surrounds the cell. The membrane consists of two layers of phospholipid molecules—called a lipid bilayer. A phospholipid molecule has a polar head and two long nonpolar hydrocarbon tails. The phospholipids are arranged so that the nonpolar tails meet in the center of the membrane. The polar heads are on both the outside surface and the inside surface, where they face the polar solutions on the outside and inside of the cell. Nonpolar cholesterol molecules are found between the tails in order to keep the nonpolar tails from moving around too much. The structure of cholesterol is shown and discussed in Section 3.14.

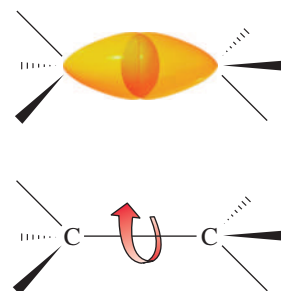
PROBLEM 30♦

The effectiveness of a barbiturate as a sedative is related to its ability to penetrate the nonpolar membrane of a cell. Which of the following barbiturates would you expect to be the more effective sedative?

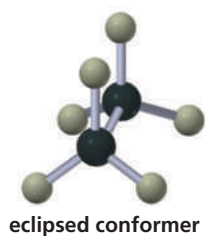
hexethal

barbital

3.9 ROTATION OCCURS ABOUT CARBON–CARBON SINGLE BONDS

We have seen that a carbon–carbon single bond (a σ bond) is formed when an sp^3 orbital of one carbon overlaps an sp^3 orbital of another carbon (Section 1.7). Figure 3.4 shows that rotation about a carbon–carbon single bond can occur without any change in the amount of orbital overlap. The different spatial arrangements of the atoms that result from rotation about a single bond are called **conformers.**

Chemists commonly use *Newman projections* to represent the three-dimensional structures that result from rotation about a σ bond. A **Newman projection** assumes that the viewer is looking along the longitudinal axis of a particular C—C bond. The carbon

▲ **Figure 3.4**
A carbon–carbon single bond is formed by the overlap of cylindrically symmetrical sp^3 orbitals, so rotation about the bond can occur without changing the amount of orbital overlap.

staggered conformer

eclipsed conformer

in front is represented by a point (where three lines are seen to intersect), and the carbon at the back is represented by a circle. The three lines emanating from each of the carbons represent its other three bonds. (Compare the three-dimensional structures shown in the margin with the two-dimensional Newman projections.)

H_3C-CH_3
ethane

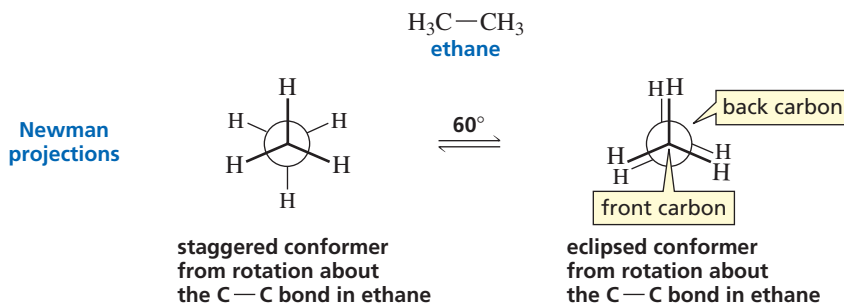
Newman projections

60°

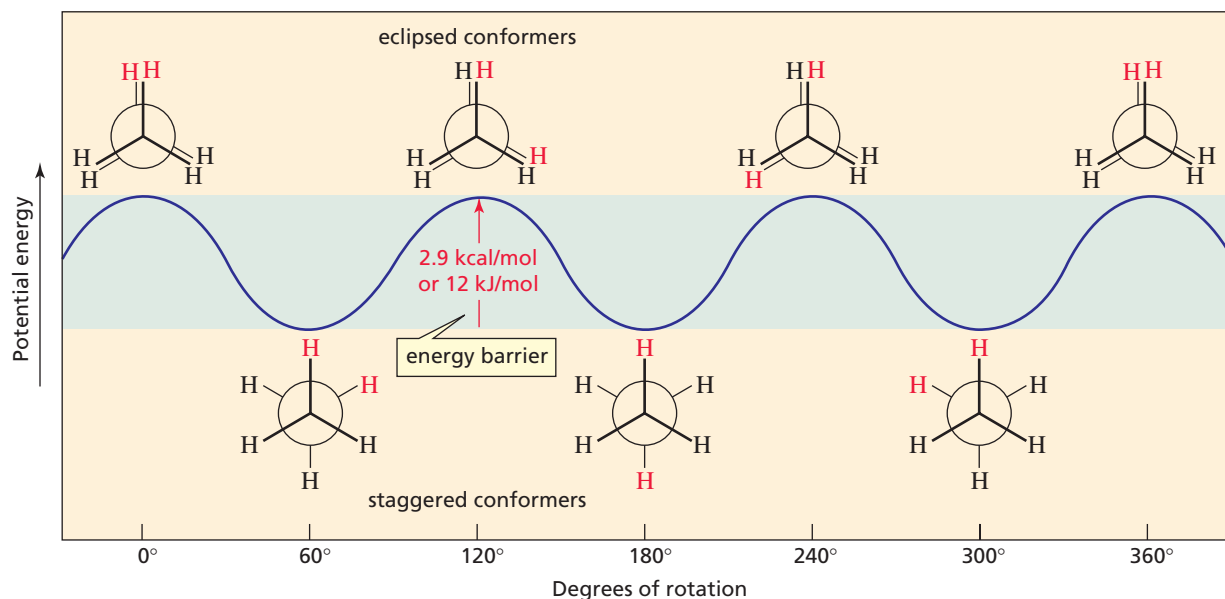
back carbon

front carbon

staggered conformer from rotation about the C—C bond in ethane

eclipsed conformer from rotation about the C—C bond in ethane

The *staggered conformer* and *eclipsed conformer* represent two extremes because rotation about a C—C bond can produce an infinite number (a continuum) of conformers between the two extremes.

A **staggered conformer** is more stable, and therefore lower in energy, than an **eclipsed conformer.** Thus, rotation about a C—C bond is not completely free since an energy barrier must be overcome when rotation occurs (Figure 3.5). However, the energy barrier in ethane is small enough (2.9 kcal/mol or 12 kJ/mol) to allow continuous rotation at room temperature.

A staggered conformer is more stable than an eclipsed conformer.

▲ **Figure 3.5**
The potential energies of all the conformers of ethane obtained in one complete 360° rotation about the C—C bond. Notice that staggered conformers are at energy minima, whereas eclipsed conformers are at energy maxima.

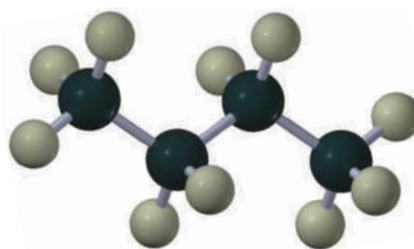
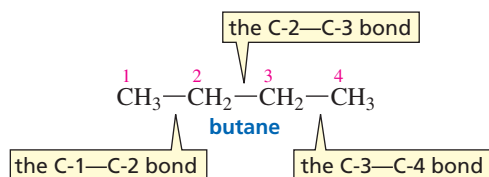
A molecule's conformation changes from staggered to eclipsed millions of times per second at room temperature. As a result, the conformers cannot be separated from each other. At any one time, approximately 99% of the ethane molecules will be in a staggered conformation because of the staggered conformer's greater stability, leaving only 1% in less stable conformations.

Butane has three carbon–carbon single bonds, and rotation can occur about each of them.

the C-2—C-3 bond

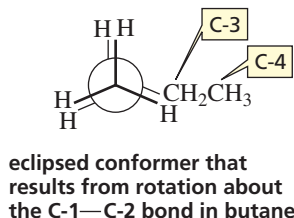
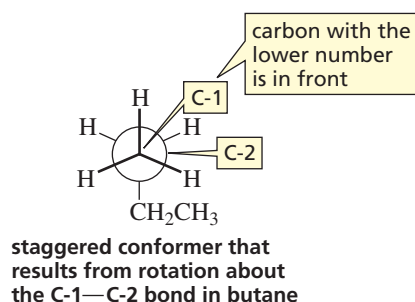
$\overset{1}{C}H_3-\overset{2}{C}H_2-\overset{3}{C}H_2-\overset{4}{C}H_3$

butane

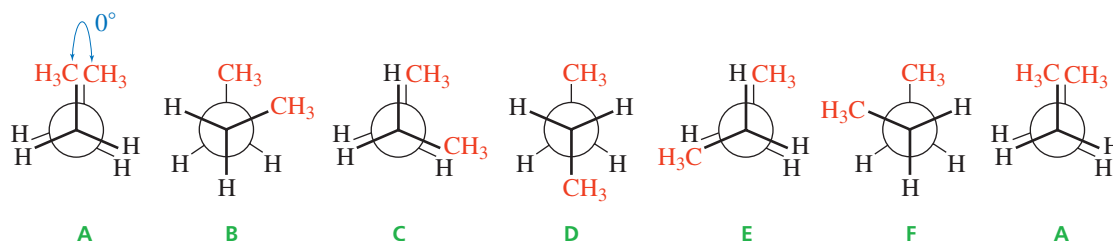
the C-1—C-2 bond the C-3—C-4 bond

ball-and-stick model of butane

The Newman projections that follow show the staggered and eclipsed conformers that result from rotation about the C-1—C-2 bond. Notice that the carbon with the lower number is placed in the foreground in a Newman projection.

staggered conformer that results from rotation about the C-1—C-2 bond in butane

eclipsed conformer that results from rotation about the C-1—C-2 bond in butane

Although the staggered conformers that result from rotation about the C-1—C-2 bond in butane all have the same energy, the staggered conformers that result from rotation about the C-2—C-3 bond do not. The staggered and eclipsed conformers that result from rotation about the C-2—C-3 bond in butane are the following:

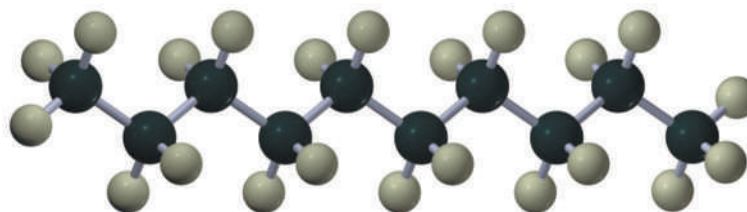
0°

A B C D E F A

Of the three staggered conformers, D has the two methyl groups as far apart as possible, so D is more stable (has lower energy) than the other two staggered conformers (B and F); D is called the **anti conformer** and B and F are called **gauche ("goesh") conformers.** (*Anti* is Greek for "opposite of"; *gauche* is French for "left.") The two gauche conformers have the same energy.

The anti and gauche conformers have different energies because of steric strain. **Steric strain** is the strain experienced by a molecule (that is, the additional energy it possesses) when atoms or groups are close enough for their electron clouds to repel each other. There is greater steric strain in a gauche conformer because the two substituents (in this case, the two methyl groups) are closer to each other. This type of steric strain is called a **gauche interaction.** In general, steric strain in molecules increases as the size of the interacting atoms or groups increases.

The eclipsed conformers also have different energies. The eclipsed conformer in which the two methyl groups are closest to each other (A) is less stable than the eclipsed conformers in which they are farther apart (C and E).

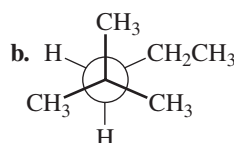
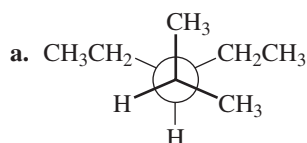
Because there is continuous rotation about all the C—C single bonds in a molecule, organic molecules are not static balls and sticks; they have many interconvertible conformers.

The relative number of molecules in a particular conformation at any one time depends on its stability—the more stable it is, the greater the fraction of molecules that will be in that conformation. Most molecules, therefore, are in staggered conformations at any given instant, and there are more anti conformers than gauche conformers. The preference for the staggered conformation gives carbon chains a tendency to adopt zigzag arrangements, as seen in the ball-and-stick model of decane.

ball-and-stick model of decane

PROBLEM 31

Convert the following Newman projections to skeletal structures and name them:

a. Front carbon: CH_3 (up), H (lower left), CH_3 (lower right); back carbon: CH_3CH_2 (upper left), CH_2CH_3 (upper right), H (down)

b. Front carbon: CH_3 (up), CH_3 (lower left), CH_3 (lower right); back carbon: H (upper left), CH_2CH_3 (upper right), H (down)

PROBLEM 32

a. Draw the three staggered conformations and the three eclipsed conformers of butane for rotation about the C-1—C-2 bond. (The carbon in the foreground in a Newman projection should have the lower number.)

b. Do the three staggered conformations have the same energy?

c. Do the three eclipsed conformations have the same energy?

PROBLEM 33

a. Draw the most stable conformation of pentane for rotation about the C-2—C-3 bond.

b. Draw the least stable conformation of pentane for rotation about the C-2—C-3 bond.

3.10 SOME CYCLOALKANES HAVE ANGLE STRAIN

We know that, ideally, an sp^3 carbon has bond angles of 109.5° (Section 1.7). In 1885, the German chemist Adolf von Baeyer, believing that all cyclic compounds were planar, proposed that the stability of a cycloalkane could be predicted by determining the difference between this ideal bond angle and the bond angle in the planar cycloalkane. For example, the bond angles in cyclopropane are 60°, representing a 49.5° deviation from 109.5°. According to Baeyer, this deviation causes **angle strain,** which decreases cyclopropane's stability.

the bond angles of planar cyclic hydrocarbons

The angle strain in a cyclopropane can be understood by looking at the overlap of the orbitals that form the σ bonds (Figure 3.6). Normal σ bonds are formed by the overlap of two sp^3 orbitals that point directly at each other. In cyclopropane, the overlapping orbitals cannot point directly at each other, so the amount of overlap between them is less than that in a normal C—C bond. This less effective overlap weakens the C—C bonds, and this weakness is what is known as angle strain.

cyclopropane

a.
good overlap
strong bond

b.
poor overlap
weak bond

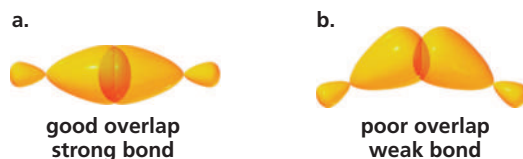



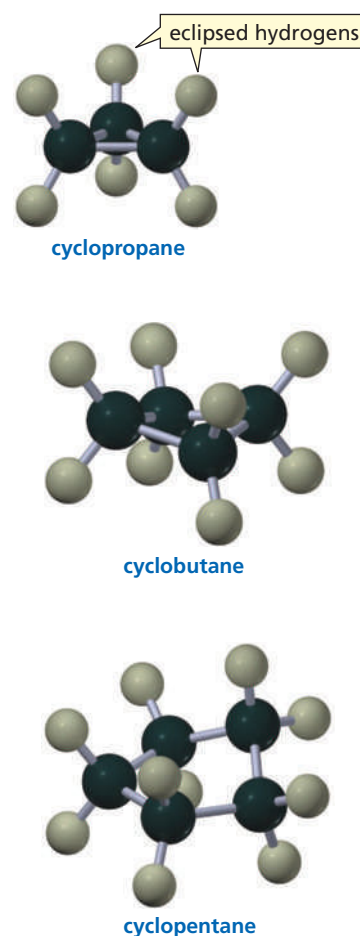
Figure 3.6
(a) Overlap of sp^3 orbitals in a normal σ bond. **(b)** Overlap of sp^3 orbitals in cyclopropane.

cyclobutane

cyclopentane

In addition to the angle strain of the C—C bonds, all the adjacent C—H bonds in cyclopropane are eclipsed rather than staggered, making it even more unstable.

Although planar cyclobutane would have less angle strain than cyclopropane, because the bond angles in cyclobutane would be only 19.5° (not 49.5°) less than the ideal bond angle, it would have eight pairs of eclipsed hydrogens, compared with six pairs in cyclopropane. Because of the eclipsed hydrogens, cyclobutane is not planar—one of the CH_2 groups is bent away from the plane defined by the other three carbons. Although bent cyclobutane has more angle strain than planar cyclobutane, the increase in angle strain is more than compensated by the decrease in eclipsed hydrogens.

If cyclopentane were planar, as Baeyer had predicted, it would have essentially no angle strain, but it would have 10 pairs of eclipsed hydrogens. Therefore, cyclopentane puckers, allowing some of the hydrogens to become nearly staggered. However, in the process, the molecule acquires some angle strain.

Von Baeyer, Barbituric Acid, and Blue Jeans

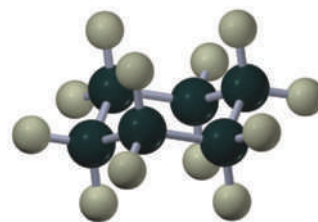
Johann Friedrich Wilhelm Adolf von Baeyer (1835–1917) was a professor of chemistry at the University of Strasbourg and later at the University of Munich. In 1864, he discovered barbituric acid—the first of a group of sedatives known as barbiturates—and named it after a woman named Barbara. Who Barbara was is not certain. Some say she was his girlfriend, but because Baeyer discovered barbituric acid in the same year that Prussia defeated Denmark, some believe he named it after Saint Barbara, the patron saint of artillerymen.

Baeyer was also the first to synthesize indigo, the dye used in the manufacture of blue jeans. He received the Nobel Prize in Chemistry in 1905 for his work in synthetic organic chemistry.

indigo dye

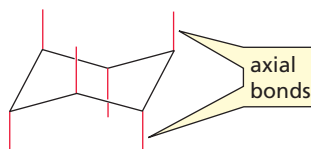
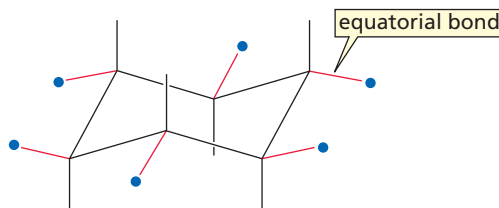
3.11 CONFORMERS OF CYCLOHEXANE

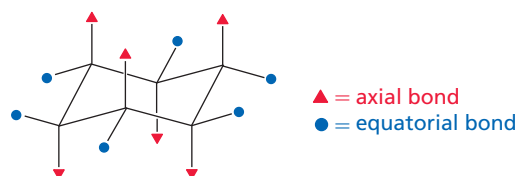
The cyclic compounds most commonly found in nature contain six-membered rings because carbon rings of that size can exist in a conformation—called a *chair conformer*—that is almost completely free of strain. All the bond angles in a **chair conformer** are 111° (which is very close to the ideal tetrahedral bond angle of 109.5°) and all the adjacent bonds are staggered (Figure 3.7).

▶ **Figure 3.7**
The chair conformer of cyclohexane, a Newman projection of the chair conformer showing that all the bonds are staggered, and a ball-and-stick model.

The chair conformer is so important that you should learn how to draw it:

1. Draw two parallel lines of the same length, slanted upward.

2. Connect the tops of the lines with a V; the left side of the V should be slightly longer than its right side. Connect the bottoms of the lines with an inverted V. (The bottom-left and top-right lines should be parallel; the top-left and bottom-right lines should be parallel.) This completes the framework of the six-membered ring.

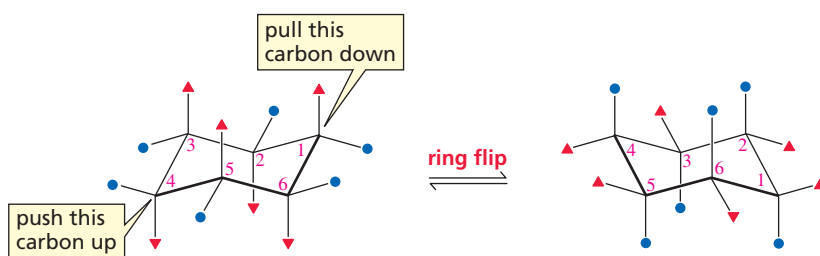
3. Each carbon has an axial bond and an equatorial bond. The **axial bonds** (red lines) are vertical and alternate above and below the ring. The axial bond on one of the uppermost carbons is up, the next is down, the next is up, and so on.

4. The **equatorial bonds** (red lines with blue balls) point outward from the ring. Because the bond angles are greater than 90°, the equatorial bonds are on a slant. If the axial bond points up, then the equatorial bond on the same carbon is on a downward slant. If the axial bond points down, then the equatorial bond on the same carbon is on an upward slant.

Notice that each equatorial bond is parallel to two ring bonds (red lines) one bond away.

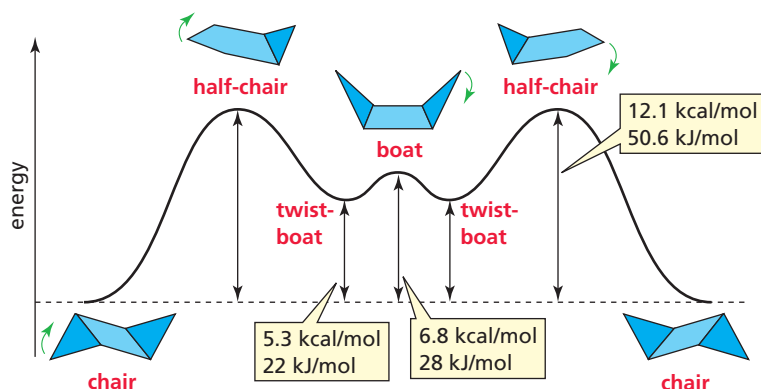
Remember that in this depiction, cyclohexane is viewed edge-on. The lower bonds of the ring are in front and the upper bonds are in back.

PROBLEM 34

Draw 1,2,3,4,5,6-hexachlorocyclohexane with

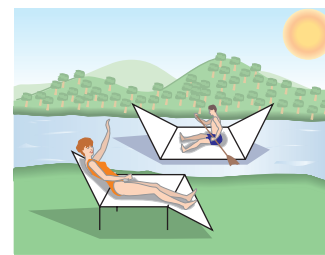
a. all the chloro groups in axial positions. **b.** all the chloro groups in equatorial positions.

Cyclohexane rapidly interconverts between two stable chair conformers because of the ease of rotation about its C—C bonds. This interconversion is called **ring flip** (Figure 3.8). When the two chair conformers interconvert, bonds that are equatorial in one chair conformer become axial in the other chair conformer, and bonds that are axial become equatorial.

Bonds that are equatorial in one chair conformer are axial in the other chair conformer.

▲ **Figure 3.8**
Ring flip causes equatorial bonds to become axial bonds and axial bonds to become equatorial bonds.

To convert from one chair conformer to the other, the bottommost carbon must be pushed up and the topmost carbon must be pulled down. The conformers that cyclohexane assumes during ring-flip are shown in Figure 3.9.

▲ **Figure 3.9**
The conformers of cyclohexane—and their relative energies—as one chair conformer interconverts to the other chair conformer.

Build a model of cyclohexane. Convert it from one chair conformer to the other by pushing the bottommost carbon up and pulling the topmost carbon down.

Because the chair conformers are so much more stable than any of the other conformers, most molecules of cyclohexane are chair conformers at any given instant. For example, for every 10,000 chair conformers of cyclohexane, there is no more than one twist-boat conformer, which is the next most stable conformer (Figure 3.9).

3.12 CONFORMERS OF MONOSUBSTITUTED CYCLOHEXANES

Unlike cyclohexane, which has two equivalent chair conformers, the two chair conformers of a monosubstituted cyclohexane (such as methylcyclohexane) are not equivalent. The methyl substituent is in an equatorial position in one conformer and in an axial position in the other (Figure 3.10), because as we have just seen, substituents that are equatorial in one chair conformer are axial in the other (Figure 3.8).

the methyl group is in an equatorial position

CH_3

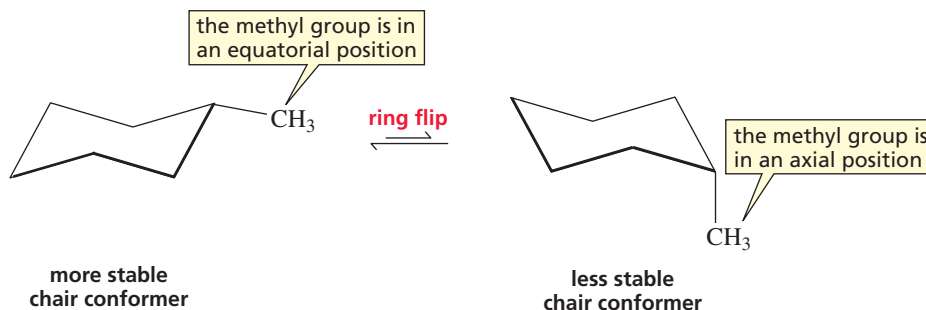
ring flip

the methyl group is in an axial position

CH_3

more stable chair conformer

less stable chair conformer

Figure 3.10
A substituent is in an equatorial position in one chair conformer and in an axial position in the other. The conformer with the substituent in the equatorial position is more stable.

The chair conformer with the methyl substituent in an equatorial position is the more stable of the two conformers because a substituent has more room and, therefore, fewer steric interactions when it is in an equatorial position. This can be understood by looking at Figure 3.11a, which shows that a methyl group in an equatorial position extends into space, away from the rest of the molecule.

a.

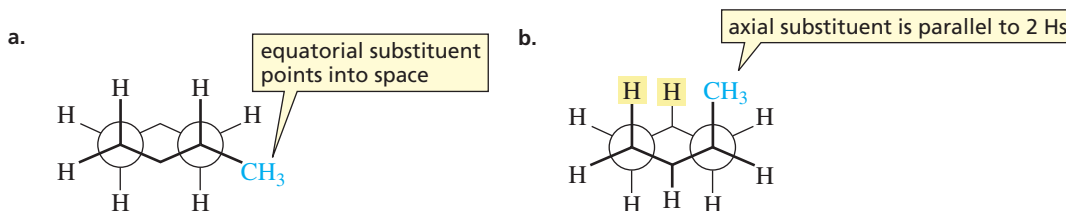
equatorial substituent points into space

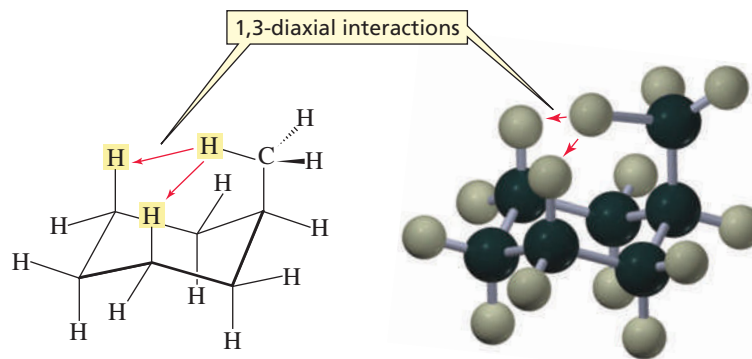
CH_3

b.

axial substituent is parallel to 2 Hs

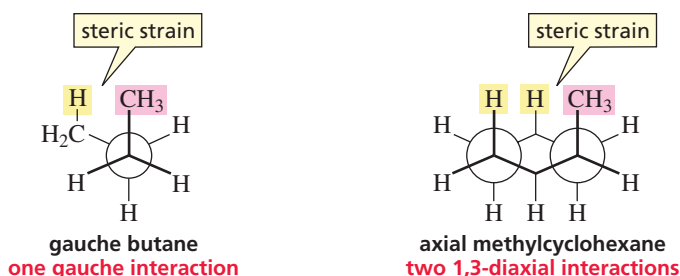
CH_3

Figure 3.11
Newman projections of methylcyclohexane:
(a) the methyl substituent is equatorial
(b) the methyl substituent is axial

In contrast, any axial substituent will be relatively close to the axial substituents on the other two carbons on the same side of the ring because all three axial bonds are parallel to each other (Figure 3.11b). Because the interacting axial substituents are in 1,3-positions relative to each other, these unfavorable steric interactions are called **1,3-diaxial interactions.**

Build a model of methylcyclohexane so you can see that a substituent has more room if it is in an equatorial position than if it is in an axial position.

A gauche conformer of butane and the axially substituted conformer of methylcyclohexane are compared in Figure 3.12. Notice that the gauche interaction in butane is the same as a 1,3-diaxial interaction in methylcyclohexane.

gauche butane
one gauche interaction

steric strain

axial methylcyclohexane
two 1,3-diaxial interactions

▲ **Figure 3.12**
Butane has one gauche interaction between a methyl group and a hydrogen, whereas methylcyclohexane has two 1,3-diaxial interactions between a methyl group and a hydrogen. (For the sake of clarity, two hydrogens in methylcyclohexane are missing.)

Because of the difference in stability of the two chair conformers, a sample of methylcyclohexane (or any other monosubstituted cyclohexane) will, at any point in time, contain more chair conformers with the substituent in an equatorial position than with the substituent in an axial position. The relative amounts of the two chair conformers depend on the substituent (Table 3.7).

Table 3.7 shows that the substituent with the greater bulk in the vicinity of the 1,3-diaxial hydrogens will have a greater preference for an equatorial position because it will have stronger 1,3-diaxial interactions.

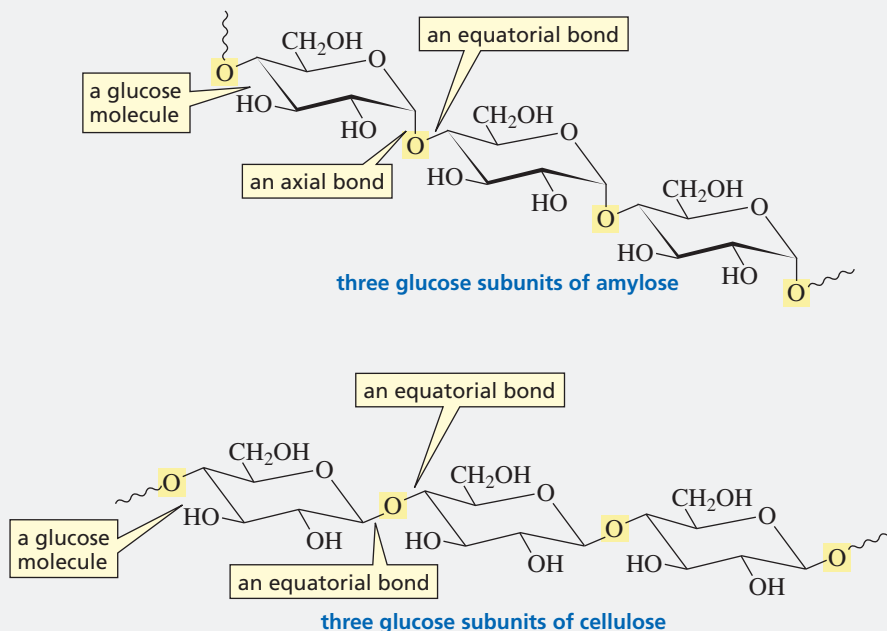
PROBLEM 35♦

At any one time, would you expect there to be more conformers with the substituent in the equatorial position in a sample of ethylcyclohexane or in a sample of isopropylcyclohexane?

Table 3.7 Equilibrium Constants for Several Monosubstituted Cyclohexanes at 25 °C

Substituent	$K_{eq} = \frac{[\text{equatorial}]}{[\text{axial}]}$
H	1
CH_3	18
CH_3CH_2	21
$CH_3CH(CH_3)$	35
$CH_3C(CH_3)_2$	4800
CN	1.4
F	1.5
Cl	2.4
Br	2.2
I	2.2
HO	5.4

Starch and Cellulose—Axial and Equatorial

Polysaccharides are compounds formed by linking many sugar molecules together. Two of the most common naturally occurring polysaccharides are amylose (an important component of starch) and cellulose. Both are formed by linking glucose molecules together. Starch, a water-soluble compound, is found in many of the foods we eat—potatoes, rice, flour, beans, corn, and peas. Cellulose, a water-insoluble compound, is the major structural component of plants. Cotton, for example, is composed of about 90% cellulose, and wood is about 50% cellulose.

foods rich in starch

cotton plant and cotton towel

How can two compounds with such different physical properties both be formed by linking together glucose molecules? If you examine their structures, you will see that the linkages in the two polysaccharides are different. In starch, an oxygen on an *axial* bond of one glucose is linked to an equatorial bond of another glucose, whereas in cellulose, an oxygen on an *equatorial* bond of one glucose is linked to an equatorial bond of another glucose. The axial bonds cause starch to form a helix that promotes hydrogen bonding with water molecules—as a result, starch is soluble in water. The equatorial bonds cause cellulose to form linear arrays that are held together by intermolecular hydrogen bonds, so it cannot form hydrogen bonds with water—as a result, cellulose is not soluble in water (Section 16.10).

Mammals have digestive enzymes that can break the axial linkages in starch but not the equatorial linkages in cellulose. Grazing animals have bacteria in their digestive tracts that possess the enzyme that can break the equatorial bonds, so cows and horses can eat hay to meet their nutritional need for glucose.

3.13 CONFORMERS OF DISUBSTITUTED CYCLOHEXANES

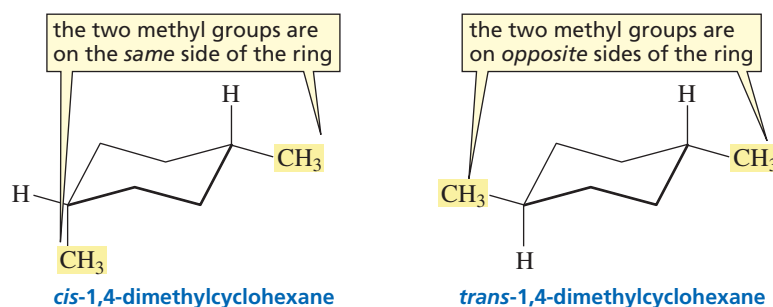
If a cyclohexane ring has two substituents, we must take both substituents into account when predicting which of the two chair conformers is more stable. Let's use 1,4-dimethylcyclohexane as an example.

First of all, note that there are two different dimethylcyclohexanes. One has both methyl substituents on the *same side* of the cyclohexane ring (both point downward)—it is called the **cis isomer** (*cis* is Latin for "on this side"). The other has the two methyl substituents on *opposite sides* of the ring (one points upward and one points downward)—it is called the **trans isomer** (*trans* is Latin for "across").

The cis isomer of a disubstituted cyclic compound has its substituents on the same side of the ring.

The trans isomer of a disubstituted cyclic compound has its substituents on opposite sides of the ring.

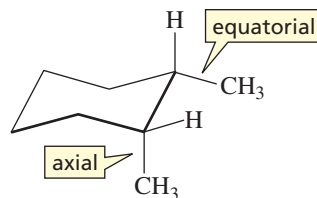
cis-1,4-dimethylcyclohexane

trans-1,4-dimethylcyclohexane

cis-1,4-Dimethylcyclohexane and *trans*-1,4-dimethylcyclohexane are examples of **cis–trans isomers** or **geometric isomers.** Geometric isomers have the same atoms, and the atoms are linked in the same order, but they have different spatial arrangements. The cis and trans isomers are different compounds with different melting and boiling points, so they can be separated from one another.

PROBLEM-SOLVING STRATEGY

Differentiating Cis–Trans Isomers

Does the cis isomer or the trans isomer of 1,2-dimethylcyclohexane have one methyl group in an equatorial position and the other in an axial position?

H
equatorial
CH_3
H
axial
CH_3

Is this the cis isomer or the trans isomer?

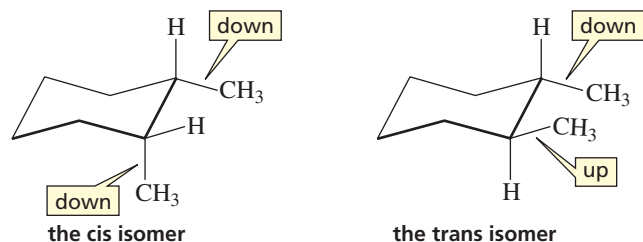
To solve this kind of problem, we need to determine whether the two substituents are on the same side of the ring (cis) or on opposite sides of the ring (trans). If the bonds bearing the substituents are both pointing upward or both pointing downward, then the compound is the cis isomer; if one bond is pointing upward and the other downward, then the compound is the

trans isomer. Because the conformer in question has both methyl groups attached to downward-pointing bonds, it is the cis isomer.

H down CH_3 H down CH_3

the cis isomer

H down CH_3 CH_3 up H

the trans isomer

The isomer that is the most misleading when drawn in two dimensions is a *trans*-1,2-disubstituted isomer. At first glance, the methyl groups of *trans*-1,2-dimethylcyclohexane (on the right in the preceding image) appear to be on the same side of the ring, so you might think the compound is the cis isomer. Closer inspection shows, however, that one bond points upward and the other downward, so we know that it is the trans isomer. Alternatively, if you look at the two axial hydrogens, they are clearly trans (one points straight up and the other straight down), so the methyl groups must also be trans.

Now use the strategy you have just learned to solve Problem 36.

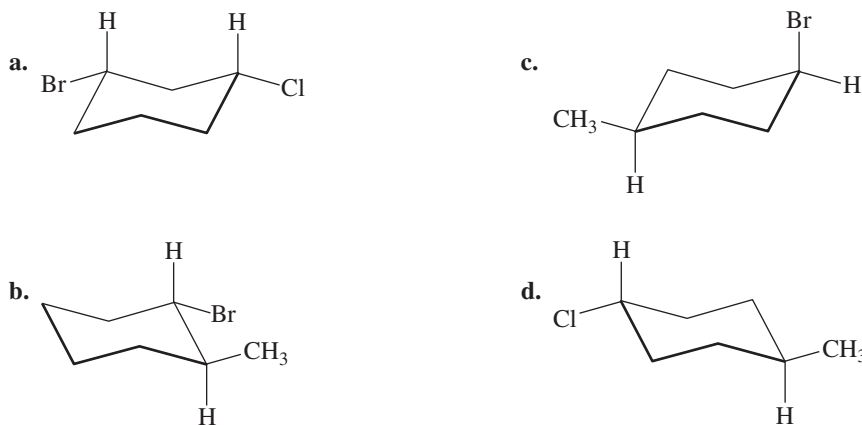
PROBLEM 36♦

Is each of the following a cis isomer or a trans isomer?

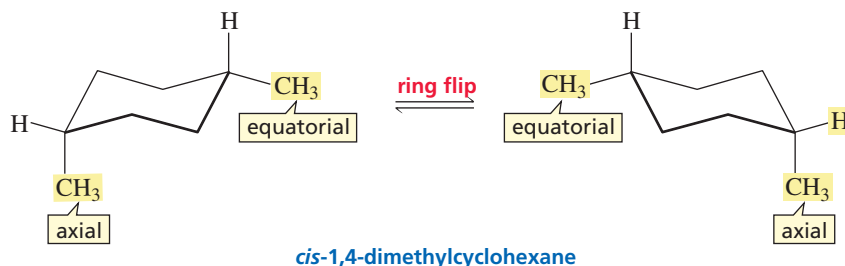
a. H H Br Cl

b. H Br CH_3 H

c. Br H CH_3 H

d. H Cl CH_3 H

Every compound with a cyclohexane ring has two chair conformers; thus, both the cis isomer and the trans isomer of a disubstituted cyclohexane have two chair conformers. Let's compare the structures of the two chair conformers of *cis*-1,4-dimethylcyclohexane to see if we can predict any difference in their stabilities.

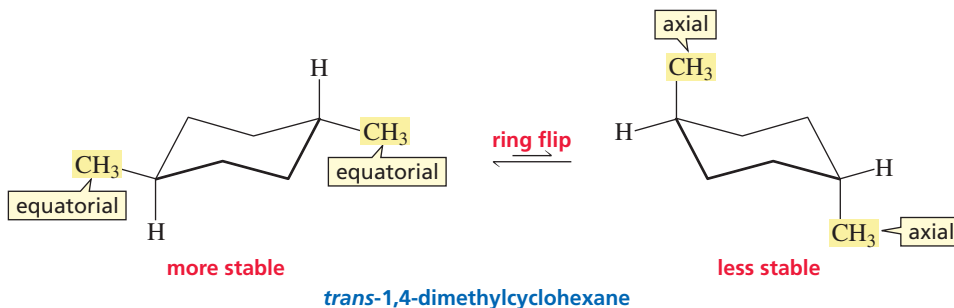
H H CH_3 equatorial CH_3 axial ring flip CH_3 equatorial H H CH_3 axial

***cis*-1,4-dimethylcyclohexane**

The conformer shown on the left has one methyl group in an equatorial position and one methyl group in an axial position. The conformer on the right also has one methyl group in an equatorial position and one methyl group in an axial position. Therefore, both chair conformers are equally stable.

In contrast, the two chair conformers of *trans*-1,4-dimethylcyclohexane have different stabilities because one has both methyl substituents in equatorial positions and the other has both methyl groups in axial positions. The conformer with both substituents in equatorial positions is more stable.

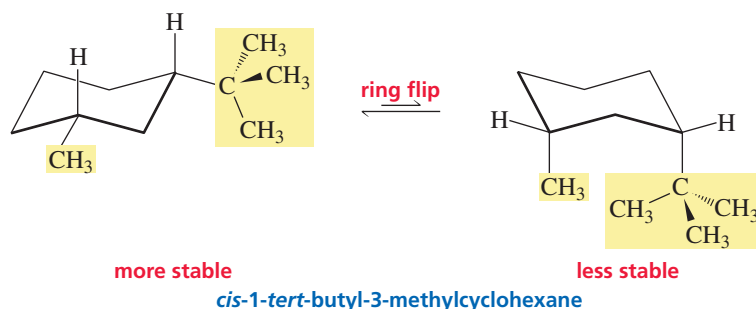
ring flip

more stable   less stable

***trans*-1,4-dimethylcyclohexane**

Now let's look at the geometric isomers of 1-*tert*-butyl-3-methylcyclohexane. Both substituents of the cis isomer are in equatorial positions in one chair conformer and both are in axial positions in the other. The conformer with both substituents in equatorial positions is more stable.

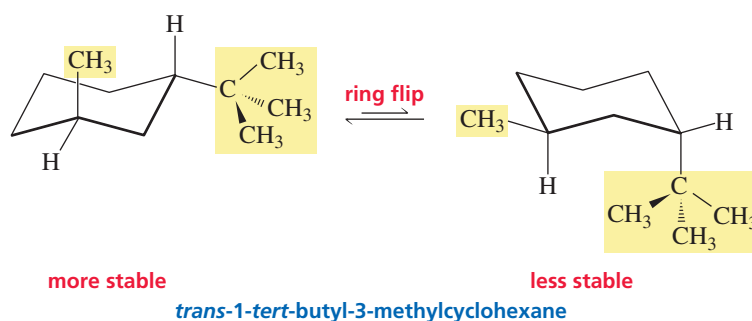
ring flip

more stable   less stable

***cis*-1-*tert*-butyl-3-methylcyclohexane**

Both chair conformers of the trans isomer have one substituent in an equatorial position and the other in an axial position. Because the *tert*-butyl group is larger than the methyl group, the 1,3-diaxial interactions will be stronger when the *tert*-butyl group is in an axial position. Therefore, the conformer with the *tert*-butyl group in an equatorial position is more stable.

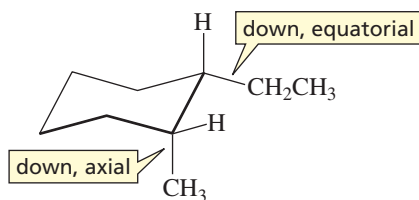
ring flip

more stable   less stable

***trans*-1-*tert*-butyl-3-methylcyclohexane**

PROBLEM 37 Solved

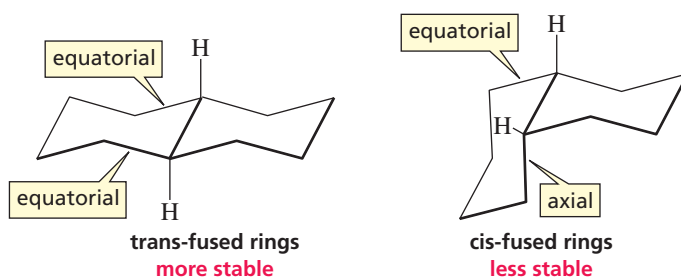
a. Draw the more stable chair conformer of *cis*-1-ethyl-2-methylcyclohexane.
b. Draw the more stable chair conformer of *trans*-1-ethyl-2-methylcyclohexane.
c. Which is more stable, *cis*-1-ethyl-2-methylcyclohexane or *trans*-1-ethyl-2-methylcyclohexane?

Solution to 37a If the two substituents of a 1,2-disubstituted cyclohexane are to be cis (on the same side of the ring), one must be in an equatorial position and the other must be in an axial position. The more stable chair conformer is the one in which the larger of the two substituents (the ethyl group) is in the equatorial position.

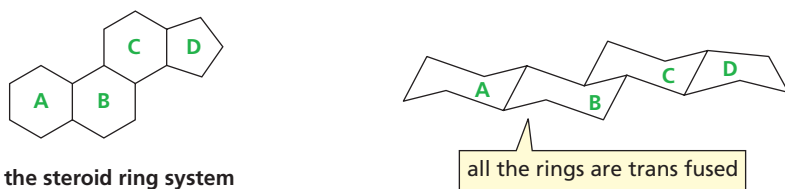
H
down, equatorial
CH_2CH_3
H
down, axial
CH_3

3.14 FUSED CYCLOHEXANE RINGS

When two cyclohexane rings are fused—**fused rings** share two adjacent carbons—one ring can be considered to be a pair of substituents bonded to the other ring. As with any disubstituted cyclohexane, the two substituents can be either cis or trans. The trans isomer (in which one substituent bond points upward and the other downward) has both substituents in the equatorial position. The cis isomer has one substituent in the equatorial position and one in the axial position. **Trans-fused** rings, therefore, are more stable than **cis-fused** rings.

equatorial
H
equatorial
H
trans-fused rings
more stable

equatorial
H
H
axial
cis-fused rings
less stable

Hormones are chemical messengers—organic compounds synthesized in glands and delivered by the bloodstream to target tissues in order to stimulate or inhibit some process. Many hormones are **steroids.** Steroids have four rings designated here by A, B, C, and D. The B, C, and D rings are all trans fused, and in most naturally occurring steroids, the A and B rings are also trans fused.

C D
A B
the steroid ring system

A B C D
all the rings are trans fused

The most abundant member of the steroid family in animals is **cholesterol,** the precursor of all other steroids. Cholesterol is an important component of cell membranes. (See the box on page 138.) Because its rings are locked in a specific conformation, it is more rigid than other membrane components.

H_3C
H_3C
H
H
H
HO
cholesterol

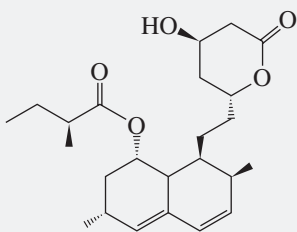
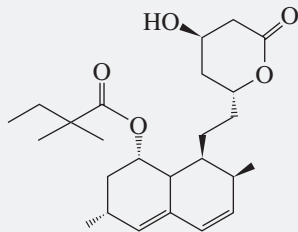
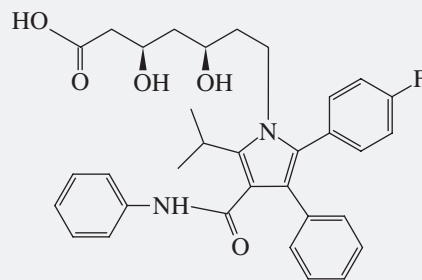
Cholesterol and Heart Disease

cholesterol (brown) blocking an artery

Cholesterol is probably the best-known steroid because of the widely publicized correlation between cholesterol levels in the blood and heart disease. Cholesterol is synthesized in the liver and is present in almost all body tissues. It is also found in many foods, but we do not require cholesterol in our diet because the body can synthesize all we need. A diet high in cholesterol can lead to high levels of cholesterol in the bloodstream, and the excess can accumulate on the walls of arteries, restricting the flow of blood. This disease of the circulatory system is known as *atherosclerosis* and is a primary cause of heart disease.

Cholesterol travels through the bloodstream packaged in particles that are classified according to their density. Low-density lipoprotein (LDL) particles transport cholesterol from the liver to other tissues. Receptors on the surfaces of cells bind LDL particles, allowing them to be brought into the cell so it can use the cholesterol. High-density lipoprotein (HDL) is a cholesterol scavenger, removing cholesterol from the surfaces of membranes and delivering it back to the liver, where it is converted into bile acids. LDL is the so-called "bad" cholesterol, whereas HDL is the "good" cholesterol. The more cholesterol we eat, the less the body synthesizes. But this does not mean that dietary cholesterol has no effect on the total amount of cholesterol in the bloodstream, because dietary cholesterol inhibits the synthesis of the LDL receptors. So the more cholesterol we eat, the less the body synthesizes, but also the less the body can get rid of by transporting it to target cells.

How High Cholesterol Is Treated Clinically

Statins are drugs that reduce serum cholesterol levels by inhibiting the enzyme that catalyzes the formation of a compound needed for the synthesis of cholesterol. As a consequence of diminished cholesterol synthesis in the liver, the liver forms more LDL receptors—the receptors that help clear LDL (the so-called "bad" cholesterol) from the bloodstream. Studies show that for every 10% that cholesterol is reduced, deaths from coronary heart disease are reduced by 15% and total death risk is reduced by 11%.

lovastatin
Mevacor®

simvastatin
Zocor®

atorvastatin
Lipitor®

Lovastatin and simvastatin are natural statins used clinically under the trade names Mevacor and Zocor. Atorvastatin (Lipitor), a synthetic statin, is the most popular statin. It has greater potency and lasts longer in the body than natural statins because the products of its breakdown are as active as the parent drug in reducing cholesterol levels. Therefore, smaller doses of the drug may be administered. In addition, Lipitor is less polar than lovastatin and simvastatin, so it persists longer in liver cells, where it is needed. Lipitor has been one of the most widely prescribed drugs in the United States for the past several years.

SOME IMPORTANT THINGS TO REMEMBER

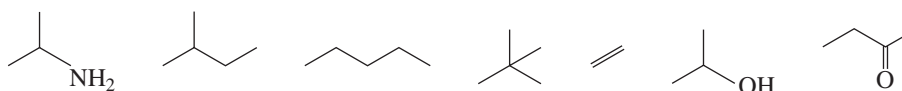
- **Alkanes** are **hydrocarbons** that contain only single bonds. Their general molecular formula is C_nH_{2n+2}.
- **Constitutional isomers** have the same molecular formula, but their atoms are linked differently.
- Alkanes are named by determining the number of carbons in their **parent hydrocarbon.** Substituents are listed as prefixes in alphabetical order, with a number to designate their position on the chain. The parent hydrocarbon is numbered in the direction that provides the name with the lowest possible number.
- **Alkyl halides** are named as substituted alkanes.
- **Systematic names** can contain numbers; **common names** never do.
- A compound can have more than one name, but a name must specify only one compound.
- Whether alkyl halides or alcohols are **primary**, **secondary**, or **tertiary** depends on whether the X (halogen) or OH group is attached to a primary, secondary, or tertiary carbon.
- Whether amines are **primary**, **secondary**, or **tertiary** depends on the number of alkyl groups attached to the nitrogen.
- The oxygen of an alcohol or an ether has the same geometry as the oxygen of water; the nitrogen of an amine has the same geometry as the nitrogen of ammonia.
- The boiling point of a compound increases as the attractive forces between its molecules—**van der Waals forces**, **dipole–dipole interactions,** and **hydrogen bonds**—increase.
- Hydrogen bonds are stronger than other dipole–dipole interactions, which are stronger than van der Waals forces.
- A **hydrogen bond** is an interaction between a hydrogen bonded to an O, N, or F and a lone pair of an O, N, or F in another molecule.
- The boiling points of alkanes increase with increasing molecular weight. Branching lowers the boiling point.
- Polar compounds dissolve in polar solvents; nonpolar compounds dissolve in nonpolar solvents.
- **Solvation** is the interaction between a solvent and a molecule or an ion dissolved in that solvent.
- The oxygen of an alcohol or an ether can drag three or four carbons into solution in water.
- Rotation about a C—C bond results in staggered and eclipsed conformers that rapidly interconvert.
- **Conformers** are different conformations of the same compound. They cannot be separated.
- A **staggered conformer** is more stable than an **eclipsed conformer.**
- The **anti conformer** is more stable than a **gauche conformer** because of **steric strain,** which is repulsion between the electron clouds of atoms or groups.
- A **gauche interaction** causes steric strain in a gauche conformer.
- Five- and six-membered rings are more stable than three- and four-membered rings because of the **angle strain** that results when bond angles deviate markedly from the ideal bond angle of 109.5°.
- Cyclohexane rapidly interconverts between two stable chair conformers—this is called **ring flip.**
- Bonds that are **axial** in one chair conformer are **equatorial** in the other and vice versa.
- A chair conformer with an equatorial substituent has less steric strain and is, therefore, more stable than a chair conformer with an axial substituent.
- An axial substituent experiences unfavorable **1,3-diaxial interactions.**
- The more stable conformer of a disubstituted cyclohexane has its substituents (or its larger substituent) on an equatorial bond.
- Cis and trans isomers (**geometric isomers**) are different compounds and can be separated.
- A **cis isomer** has its two substituents on the same side of the ring; a **trans isomer** has its substituents on opposite sides of the ring.

PROBLEMS

38. Draw a condensed structure and a skeletal structure for each of the following compounds:

a. *sec*-butyl *tert*-butyl ether
b. isoheptyl alcohol
c. *sec*-butylamine
d. 1,1-dimethylcyclohexane
e. triethylamine
f. 5,5-dibromo-2-methyloctane

39. List the following compounds from highest boiling to lowest boiling:

NH_2 OH O

40. a. What is each compound's systematic name?
b. Draw a skeletal structure for each condensed structure given, and draw a condensed structure for each skeletal structure given in the following list:

1. $(CH_3)_3CCH_2CH_2CH_2CH(CH_3)_2$

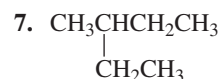
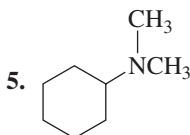
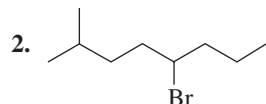
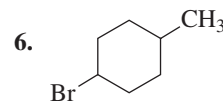
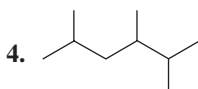
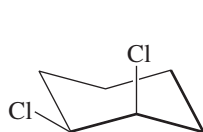
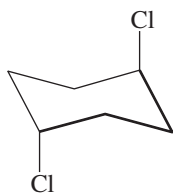
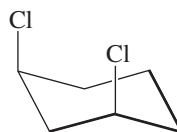
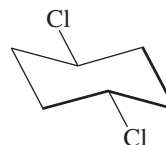
2. Br

3. $(CH_3CH_2)_4C$

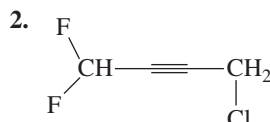
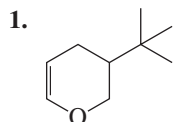
4.

5. CH_3 NCH_3

6. CH_3 Br

7. $CH_3CHCH_2CH_3$ with CH_2CH_3

41. Which of the following represents a cis isomer?

42. a. How many primary carbons does each of the following compounds have?
b. How many secondary carbons does each one have?
c. How many tertiary carbons does each one have?

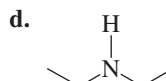
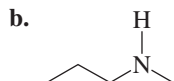
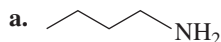
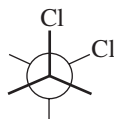
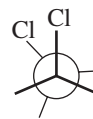
1. O

2. F F CH—≡—CH_2 Cl

43. Name the following amines and state whether they are primary, secondary, or tertiary:

a. NH_2

b. H N

c. NH_2

d. H N

44. Which of the following conformers of 2,3-dichloro-2,3-dimethylbutane is the most stable?

45. What is each compound's name?

a.

b. CHF_2COOH

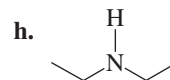
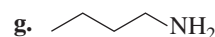
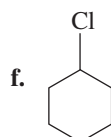
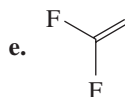
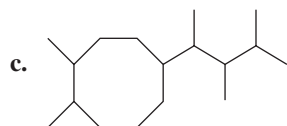
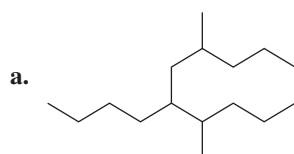
c.

d. CH_3OCH_2

e.

f.

g. NH_2

h. H N

46. Draw the structural formula for an alkane that has
a. six carbons, all secondary.
b. eight carbons and only primary hydrogens.
c. seven carbons with two isopropyl groups.

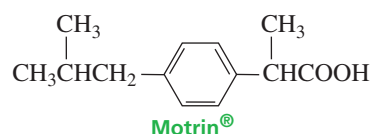
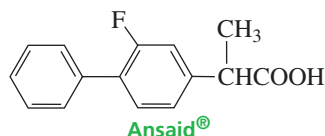
47. Which has
a. the higher boiling point: 1-bromopentane or 1-bromohexane?
b. the higher boiling point: pentyl chloride or isopentyl chloride?
c. the greater solubility in water: 1-butanol or 1-pentanol?
d. the higher boiling point: hexyl alcohol or methyl pentyl ether?
e. the higher melting point: hexane or isohexane?
f. the higher boiling point: pentyl chloride or pentyl alcohol?
g. the higher boiling point: 1-bromopentane or 1-chloropentane?
h. the higher boiling point: diethyl ether or butyl alcohol?
i. the greater density: heptane or octane?
j. the higher boiling point: isopentyl alcohol or isopentylamine?
k. the higher boiling point: hexylamine or dipropylamine?

48. Ansaid and Motrin belong to the group of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs). Both are only slightly soluble in water, but one is a little more soluble than the other. Which of the drugs has the greater solubility in water?

F, CH_3, CHCOOH

Ansaid®

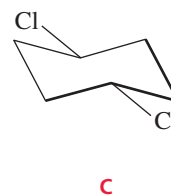
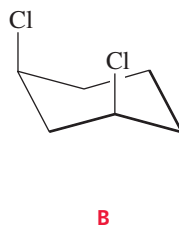
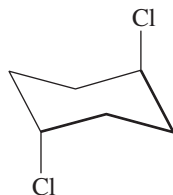
CH_3, CH_3CHCH_2, CH_3, CHCOOH

Motrin®

49. A student was given the structural formulas of several compounds and was asked to give them systematic names. How many did the student name correctly? Correct those that are misnamed.
a. 2,2-dimethyl-4-ethylheptane
b. isopentyl bromide
c. 3,3-dichlorooctane
d. 5-ethyl-2-methylhexane
e. 3,5-dimethylhexane
f. 2-methyl-3-propylpentane

50. Which of the following conformers has the highest energy (is the least stable)?

A

B

C

51. Give the systematic names for all alkanes with molecular formula C_7H_{16} that do not have any secondary hydrogens.

52. Draw skeletal structures for the following:
a. 5-ethyl-2-methyloctane
b. 1,3-dimethylcyclohexane
c. 2,3,3,4-tetramethylheptane
d. propylcyclopentane

53. Which of the following statements can be used to prove that carbon is tetrahedral?
a. Methyl bromide does not have constitutional isomers.
b. Tetrachloromethane does not have a dipole moment.
c. Dibromomethane does not have constitutional isomers.

54. For rotation about the C-3 — C-4 bond of 2-methylhexane, do the following:
a. Draw the Newman projection of the most stable conformer.
b. Draw the Newman projection of the least stable conformer.
c. About which other carbon–carbon bonds may rotation occur?
d. How many of the carbon–carbon bonds in the compound have staggered conformers that are all equally stable?

55. Draw all the isomers that have molecular formula $C_5H_{11}Br$. (*Hint*: There are eight.)
a. Give the systematic name for each of the isomers.
b. Give a common name for each isomer that has a common name.
c. How many of the isomers are primary alkyl halides?
d. How many of the isomers are secondary alkyl halides?
e. How many of the isomers are tertiary alkyl halides?

56. What is each compound's systematic name?

a.

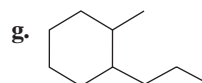
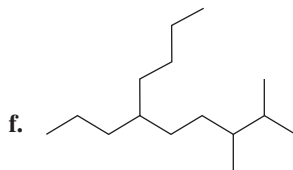
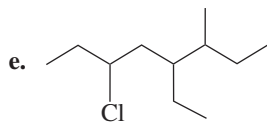
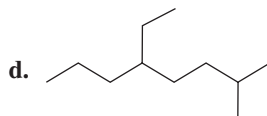
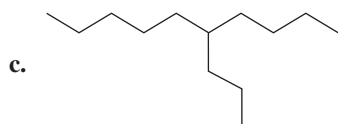
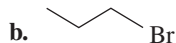
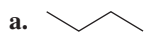
b. Br

c.

d.

e. Cl

f.

g.

57. Draw the two chair conformers for each of the following, and indicate which conformer is more stable:
a. *cis*-1-ethyl-3-methylcyclohexane
b. *trans*-1-ethyl-2-isopropylcyclohexane
c. *trans*-1-ethyl-2-methylcyclohexane
d. *cis*-1,2-diethylcyclohexane
e. *cis*-1-ethyl-3-isopropylcyclohexane
f. *cis*-1-ethyl-4-isopropylcyclohexane

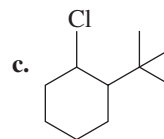
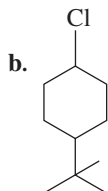
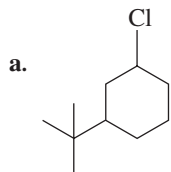
58. Draw the nine constitutional isomers with molecular formula C_7H_{16}.

59. Why are lower molecular weight carboxylic acids more soluble in water than higher molecular weight carboxylic acids?

60. Draw both the cis and the trans isomers of the following. For each of the following compounds, is the cis isomer or the trans isomer more stable?

a. Cl

b. Cl

c. Cl

61. How many alkanes have molecular formula C_5H_{12}? Draw their structures and name them.

62. Using Newman projections, draw the most stable conformation for the following:
a. 3-methylpentane, viewed along the C-2 — C-3 bond
b. 3-methylhexane, viewed along the C-3 — C-4 bond

63. For each of the following disubstituted cyclohexanes, indicate whether the substituents in its two chair conformers would be both equatorial in one chair conformer and both axial in the other *or* one equatorial and one axial in each of the chair conformers:
a. *cis*-1,2- **b.** *trans*-1,2- **c.** *cis*-1,3- **d.** *trans*-1,3- **e.** *cis*-1,4- **f.** *trans*-1,4-

64. Which will have a higher percentage of the diequatorial-substituted conformer compared with the diaxial-substituted conformer: *trans*-1,4-dimethylcyclohexane or *cis*-1-*tert*-butyl-3-methylcyclohexane?

65. Draw the most stable conformer of the following molecule. (A solid wedge points out of the plane of the paper toward the viewer. A hatched wedge points back from the plane of the paper away from the viewer.)

CH_3
H_3C
H_3C

66. What is each compound's systematic name?

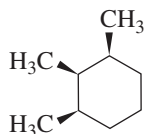
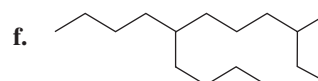
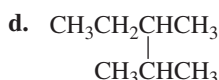
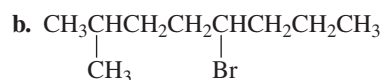
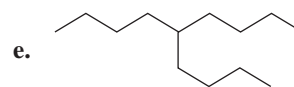
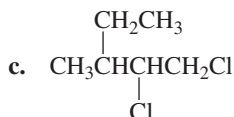
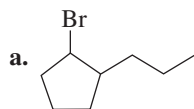
a. Br

b. $CH_3CHCH_2CH_2CHCH_2CH_2CH_3$ (with CH_3 and Br substituents)

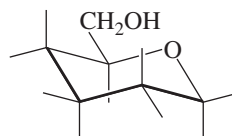
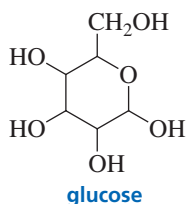
c. $CH_3CHCHCH_2Cl$ (with CH_2CH_3 and Cl substituents)

d. $CH_3CH_2CHCH_3$ (with CH_3CHCH_3 substituent)

e.

f.

67. The most stable form of glucose (blood sugar) is a six-membered ring in a chair conformation with its five substituents all in equatorial positions. Draw the most stable conformer of glucose by putting the OH groups on the appropriate bonds in the structure on the right.

CH_2OH
HO
O
HO
OH
OH

glucose

68. Bromine is a larger atom than chlorine, but the equilibrium constants in Table 3.7 indicate that a chloro substituent has a greater preference for the equatorial position than does a bromo substituent. Suggest an explanation for this fact.

69. One of the chair conformers of *cis*-1,3-dimethylcyclohexane is 5.4 kcal/mol less stable than the other. Given that a 1,3-diaxial interaction between a CH_3 and an H is 0.87 kcal/mol, how much steric strain does a 1,3-diaxial interaction between two methyl groups introduce into the conformer?

70. Using the data obtained in Problem 69, calculate the amount of steric strain in each of the chair conformers of 1,1,3-trimethylcyclohexane. Which conformer would predominate at equilibrium?

71. **a.** Draw a potential energy diagram for rotation about the Ci C bond of 1,2-dichloroethane through 360, starting with the least stable conformer. The anti conformer is 1.2 kcal/mol more stable than a gauche conformer. A gauche conformer has two energy barriers, 5.2 kcal/mol and 9.3 kcal/mole.

b. Draw the conformer that would be present in greatest concentration.

c. How much more stable is the most stable staggered conformer than the most stable eclipsed conformer?

d. How much more stable is the most stable staggered conformer than the least stable eclipsed conformer?

4 Isomers: The Arrangement of Atoms in Space

mirror image

In this chapter, we will see why interchanging two groups bonded to a carbon can have a profound effect on the physiological properties of a compound. For example, interchanging a hydrogen and a methyl group converts the active ingredient in Vicks vapor inhaler to methamphetamine, the street drug known as speed. The same change converts the active ingredient in Aleve, a common drug for pain, to a compound that is highly toxic to the liver.

We will now turn our attention to **isomers**—compounds with the same molecular formula but different structures. Isomers fall into two main classes: *constitutional isomers* and *stereoisomers.*

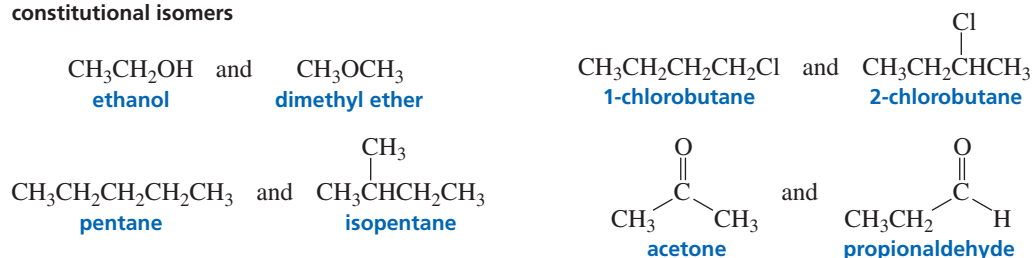
Constitutional isomers differ in the way their atoms are connected. For example, ethanol and dimethyl ether are constitutional isomers because they both have molecular formula C_2H_6O, but their atoms are connected differently (the oxygen in ethanol is bonded to a carbon and to a hydrogen, whereas the oxygen in dimethyl ether is bonded to two carbons).

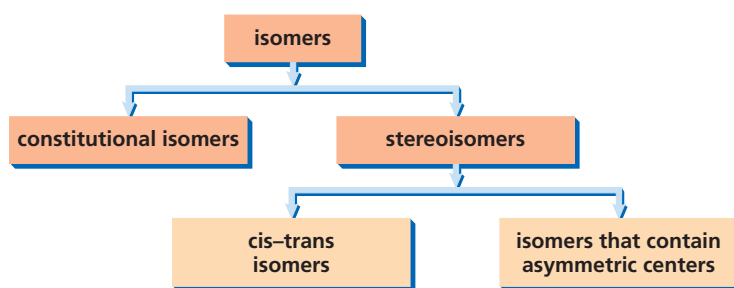
constitutional isomers

CH_3CH_2OH and CH_3OCH_3
ethanol, dimethyl ether

$CH_3CH_2CH_2CH_2Cl$ and $CH_3CH_2CH(Cl)CH_3$
1-chlorobutane, 2-chlorobutane

$CH_3CH_2CH_2CH_2CH_3$ and $CH_3CH(CH_3)CH_2CH_3$
pentane, isopentane

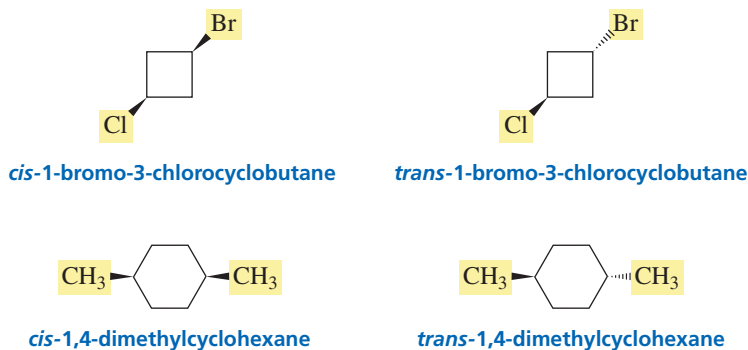
$CH_3C(=O)CH_3$ and $CH_3CH_2C(=O)H$
acetone, propionaldehyde

Unlike constitutional isomers, the atoms in stereoisomers are connected in the same way. **Stereoisomers** differ in the way their atoms are arranged in space. Like constitutional isomers, stereoisomers can be separated because they are different compounds; they can

interconvert only if bonds are broken. There are two kinds of stereoisomers: *cis–trans isomers* and isomers that contain *asymmetric centers.*

PROBLEM 1♦

a. Draw three constitutional isomers with molecular formula C_3H_8O.
b. How many constitutional isomers can you draw for $C_4H_{10}O$?

4.1 CIS–TRANS ISOMERS RESULT FROM RESTRICTED ROTATION

The first type of stereoisomers we will look at are **cis–trans isomers** (also called **geometric isomers**). These isomers result from restricted rotation. Restricted rotation can be caused either by a *cyclic structure* or by a *double bond.*

We have seen that, as a result of restricted rotation about the bonds in a ring, cyclic compounds with two substituents bonded to different carbons have cis and trans isomers (Section 3.13). *The cis isomer has its substituents on the same side of the ring; the trans isomer has its substituents on opposite sides of the ring.* (A solid wedge represents a bond that points out of the plane of the paper toward the viewer, and a hatched wedge represents a bond that points into the plane of the paper away from the viewer.)

PROBLEM 2

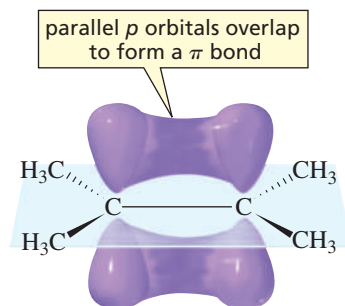
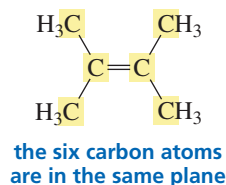
Draw the cis and trans isomers for the following:

a. 1-bromo-4-chlorocyclohexane **b.** 1-ethyl-3-methylcyclobutane

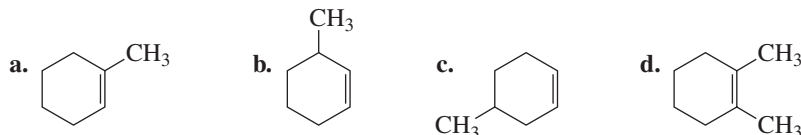
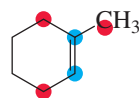
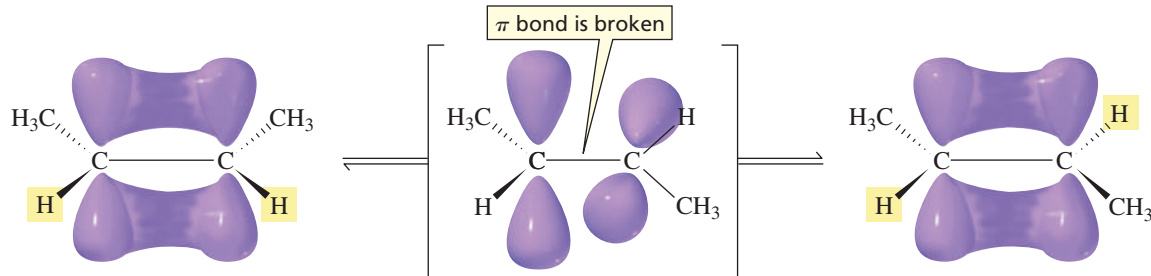
Compounds with carbon–carbon double bonds can also have cis and trans isomers. The structure of the smallest compound with a carbon–carbon double bond (ethene) was described in Section 1.8, where we saw that the double bond was composed of a σ bond and a π bond. We saw that the π bond was formed by side-to-side overlap of two parallel *p* orbitals—one from each carbon. Other compounds with carbon–carbon double bonds have similar structures.

Because three points determine a plane, each sp^2 carbon and the two atoms singly bonded to it lie in a plane. In order to achieve maximum orbital–orbital overlap, the two *p* orbitals must be parallel to each other. For the two *p* orbitals to be parallel, all six atoms of the double-bond system must be in the same plane.

H_3C CH_3
C=C
H_3C CH_3

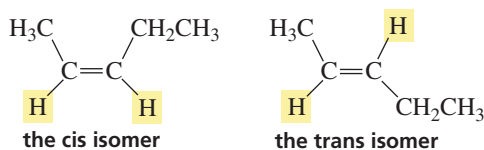
the six carbon atoms are in the same plane

PROBLEM 3♦ Solved

How many carbons are in the planar double-bond system in each of the following compounds?

a. CH_3 **b.** CH_3 **c.** CH_3 **d.** CH_3 CH_3

Solution to 3a Five carbons are in its planar double-bond system: the two sp^2 carbons (indicated by blue dots) and the three carbons bonded to the sp^2 carbons (indicated by red dots).

Rotation about a double bond does not readily occur, because it can happen only if the π bond breaks—that is, only if the p orbitals are no longer parallel (Figure 4.1). Consequently, the energy barrier to rotation about a carbon–carbon double bond is much greater (about 62 kcal/mol) than the energy barrier to rotation about a carbon–carbon single bond, which is only about 2.9 kcal/mol (Section 3.9).

▲ Figure 4.1
Rotation about the carbon–carbon double bond breaks the π bond.

Because of the high energy barrier to rotation about a carbon–carbon double bond, a compound with a carbon–carbon double bond can exist in two distinct forms—the hydrogens bonded to the sp^2 carbons can be on the same side of the double bond or on opposite sides of the double bond.

H_3C CH_2CH_3
C=C
H H
the cis isomer

H_3C H
C=C
H CH_2CH_3
the trans isomer

The compound with the hydrogens on the same side of the double bond is called the **cis isomer;** the compound with the hydrogens on opposite sides of the double bond is called the **trans isomer.** Notice that the cis and trans isomers have the same molecular formula and the same bonded atoms but have different *configurations*—they differ in the way their atoms are oriented in space.

Cis and trans isomers can be separated from each other because they are different compounds with different physical properties—for example, they have different boiling points and different dipole moments.

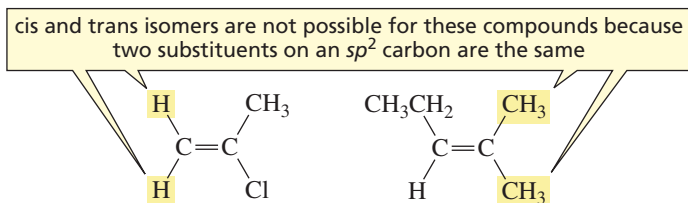
H_3C, CH_3 / C=C / H, H
the cis isomer
bp = 3.7 °C

H_3C, H / C=C / H, CH_3
the trans isomer
bp = 0.9 °C

Cl, Cl / C=C / H, H
the cis isomer
bp = 60.3 °C

Cl, H / C=C / H, Cl
the trans isomer
bp = 47.5 °C

Notice that the trans isomers, unlike the cis isomers, have dipole moments (μ) of zero because the dipole moments of their individual bonds cancel (Section 1.15).

If one of the sp^2 carbons is attached to two identical substituents, then the compound cannot have cis and trans isomers.

Notice that switching two groups on one of the sp^2 carbons (for example, the H and CH_3 of the cis isomer on the top left of this page) converts a cis isomer to a trans isomer. Therefore, if the two groups on an sp^2 carbon are the same, the compound does not have cis and trans isomers.

PROBLEM 4

a. Which of the following compounds can exist as cis–trans isomers?
b. For those compounds that can exist as cis and trans isomers, draw and label the isomers.

1. $CH_3CH{=}CHCH_2CH_2CH_3$

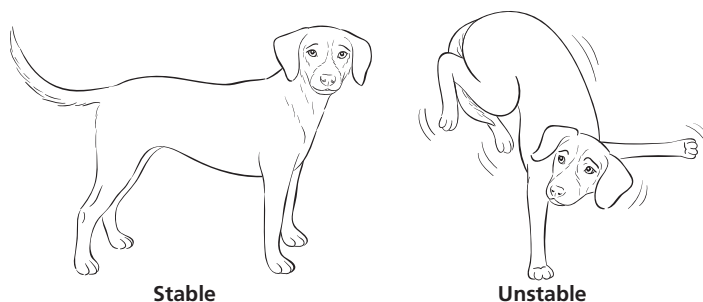
2. $CH_3CH_2C{=}CHCH_3$ (with CH_2CH_3 on the C)

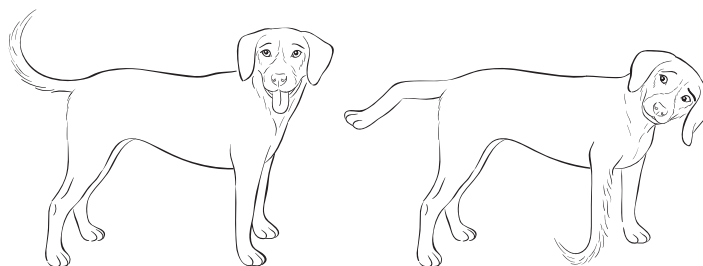
3. $CH_3CH{=}CHCH_3$

4. $CH_3CH_2CH{=}CH_2$

Do not confuse the terms *conformation* and *configuration.*

- Conformations (or conformers) are different spatial arrangements of the same compound (for example, anti and gauche conformers; Section 3.9). They cannot be separated. Some conformations are more stable than others.

Different Conformations

- Compounds with different configurations (stereoisomers) are different compounds (for example, cis and trans isomers). They can be separated from each other. Bonds have to be broken to interconvert compounds with different configurations.

Different Configurations

PROBLEM 5

Draw skeletal structures for all the compounds in Problem 4, including any cis–trans isomers.

PROBLEM 6♦

Draw three compounds with molecular formula C_5H_{10} that have carbon–carbon double bonds but do not have cis–trans isomers.

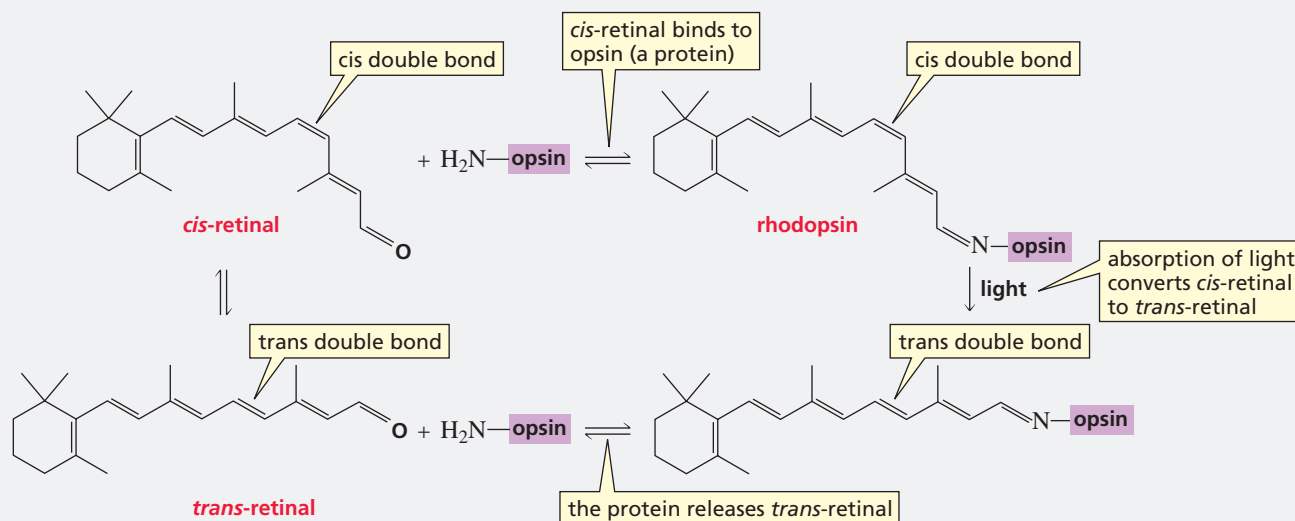
Cis–Trans Interconversion in Vision

Our ability to see depends in part on an interconversion of cis and trans isomers that takes place in our eyes. A protein called opsin binds to *cis*-retinal (formed from vitamin A) in photoreceptor cells (called rod cells) in the retina to form rhodopsin. When rhodopsin absorbs light, a double bond interconverts between the cis and trans configurations, triggering a nerve impulse that plays an important role in vision. *trans*-Retinal is then released from opsin. *trans*-Retinal isomerizes back to *cis*-retinal and another cycle begins. To trigger the nerve impulse, a group of about 500 rod cells must register five to seven rhodopsin isomerizations per cell within a few tenths of a second.

view inside the human eye

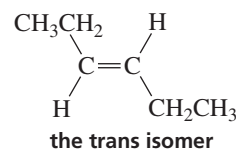
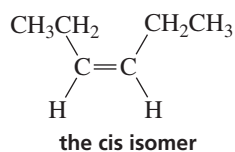
cis double bond — *cis*-retinal + H_2N—opsin ⇌ rhodopsin (*cis*-retinal binds to opsin (a protein); cis double bond)

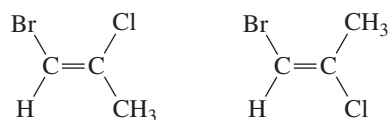
absorption of light converts *cis*-retinal to *trans*-retinal (light)

trans-retinal (trans double bond) + H_2N—opsin ⇌ N—opsin (trans double bond; the protein releases *trans*-retinal)

4.2 DESIGNATING GEOMETRIC ISOMERS USING THE *E,Z* SYSTEM

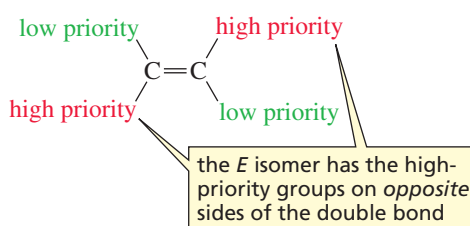
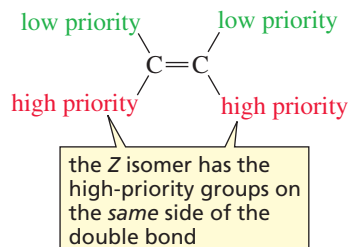
We have just seen that the geometric isomers of an alkene are designated by the terms *cis* and *trans*: *if the hydrogens are on the same side of the double bond, it is the cis isomer; if the hydrogens are on opposite sides of the double bond, it is the trans isomer* (Section 4.1).

CH_3CH_2, CH_2CH_3 / C=C / H, H — **the cis isomer**

CH_3CH_2, H / C=C / H, CH_2CH_3 — **the trans isomer**

But how do we designate the geometric isomers of the following compound?

Br, Cl / C=C / H, CH_3 Br, CH_3 / C=C / H, Cl

Which isomer is cis and which is trans?

The *E,Z* system of nomenclature was devised for alkenes that do not have a hydrogen attached to each of the sp^2 carbons.*

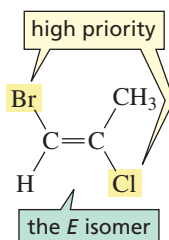
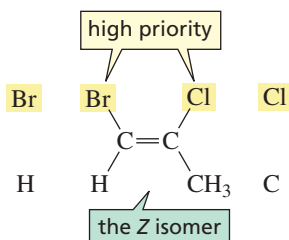
To name an isomer by the *E,Z* system, we first determine the relative priorities of the two groups bonded to one of the sp^2 carbons and then the relative priorities of the two groups bonded to the other sp^2 carbon. (The rules for assigning relative priorities are explained below.)

The *Z* isomer has the high-priority groups on the same side.

The *E* isomer has the high-priority groups on opposite sides.

If the two high-priority groups (one from each carbon) are on the same side of the double bond, the isomer is the *Z* isomer (*Z* is for *zusammen*, German for "together"). If the high-priority groups are on opposite sides of the double bond, the isomer is the *E* isomer (*E* is for *entgegen*, German for "opposite").

The relative priorities of the two groups bonded to an sp^2 carbon are determined using the following rules:

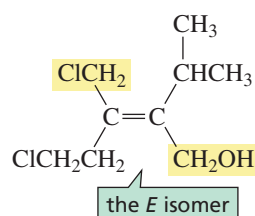
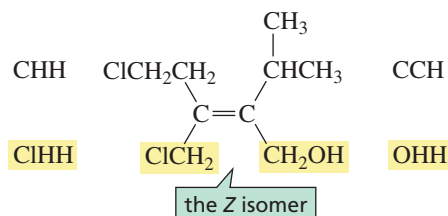
1. The relative priorities depend on the atomic numbers of the atoms bonded directly to the sp^2 carbon. The greater the atomic number, the higher the priority.

   For example, in the isomer below on the left, the sp^2 carbon on the left is bonded to a Br and to an H; Br has a greater atomic number than H, so **Br** has the higher priority.

The greater the atomic number of the atom bonded to the sp^2 carbon, the higher the priority of the substituent.

   The sp^2 carbon on the right is bonded to a Cl and to a C; Cl has the greater atomic number, so **Cl** has the higher priority. (Notice that you use the atomic number of C, not the mass of the CH_3 group, because the priorities are based on the atomic numbers of atoms, *not* on the masses of groups.)

   Thus, the isomer on the left has the high-priority groups (Br and Cl) on the same side of the double bond, so it is the *Z* **isomer.** (Zee groups are on Zee Zame Zide.) The isomer on the right has the high-priority groups on opposite sides of the double bond, so it is the *E* **isomer.**

2. If the two atoms attached to an sp^2 carbon are the same (there is a tie), then consider the atomic numbers of the atoms that are attached to the "tied" atoms.

   For example, in the isomer shown next on the left, both atoms bonded to the sp^2 carbon on the left are carbons (in a CH_2Cl group and a CH_2CH_2Cl group), so there is a tie.

If the atoms attached to the sp^2 carbon are the same, the atoms attached to the tied atoms are compared; the one with the greater atomic number belongs to the group with the higher priority.

*The IUPAC prefers the *E* and *Z* designations because they can be used for all alkene isomers. Many chemists, however, continue to use the "cis" and "trans" designations for simple molecules.

The C of the CH_2Cl group is bonded to **Cl, H, H,** and the C of the CH_2CH_2Cl group is bonded to **C, H, H.** Cl has a greater atomic number than C, so the CH_2Cl group has the higher priority.

Both atoms attached to the sp^2 carbon on the right are Cs (in a CH_2OH group and a $CH(CH_3)_2$ group), so there is a tie on this side as well. The C of the CH_2OH group is bonded to **O, H, H,** and the C of the $CH(CH_3)_2$ group is bonded to **C, C, H.** Of these six atoms, O has the greatest atomic number, so $\mathbf{CH_2OH}$ has the higher priority. (Note that you do not add the atomic numbers—you take the single atom with the greatest atomic number.) The *E* and *Z* isomers are as shown above.

3. If an atom is doubly bonded to another atom, the priority system treats it as if it were singly bonded to two of those atoms. If an atom is triply bonded to another atom, the priority system treats it as if it were singly bonded to three of those atoms.

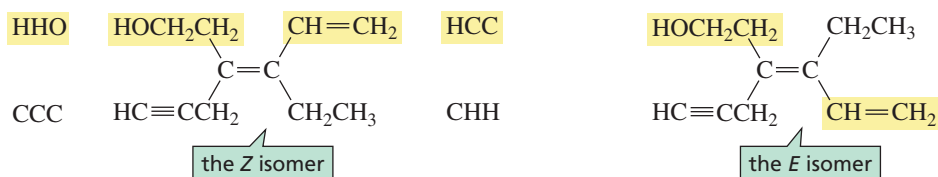
If an atom is doubly bonded to another atom, treat it as if it were singly bonded to two of those atoms.

If an atom is triply bonded to another atom, treat it as if it were singly bonded to three of those atoms.

Cancel atoms that are identical in the two groups; use the remaining atoms to determine the group with the higher priority.

For example, in the isomer shown next on the left, the sp^2 carbon on the left is bonded to a CH_2CH_2OH group and to a $CH_2C{\equiv}CH$ group:

HHO $HOCH_2CH_2$ $CH{=}CH_2$ HCC
C=C
CCC $HC{\equiv}CCH_2$ CH_2CH_3 CHH
the *Z* isomer

$HOCH_2CH_2$ CH_2CH_3
C=C
$HC{\equiv}CCH_2$ $CH{=}CH_2$
the *E* isomer

Because the atoms bonded to the sp^2 carbon are both carbons, there is a tie. Each of the carbons is bonded to **C, H, H,** so there is another tie. We turn our attention to the groups attached to the CH_2 groups to break the tie. One of these groups is CH_2OH, and the other is $C{\equiv}CH$; the C of the CH_2OH group is bonded to **H, H, O;** the triple-bonded C is considered to be bonded to **C, C, C.** Of the six atoms, O has the greatest atomic number, so $\mathbf{CH_2CH_2OH}$ has the higher priority.

Both atoms bonded to the sp^2 carbon on the right are Cs, so they are tied. The first carbon of the CH_2CH_3 group is bonded to **C, H, H;** the first carbon of the $CH{=}CH_2$ group is bonded to an H and doubly bonded to a C, so it is considered to be bonded to **H, C, C.** One **C** cancels in each of the two groups, leaving **H** and **H** in the CH_2CH_3 group and **H** and **C** in the $CH{=}CH_2$ group. C has a greater atomic number than H, so $\mathbf{CH{=}CH_2}$ has the higher priority.

PROBLEM 7♦

Assign relative priorities to each set of substituents:

a. —Br —I —OH $—CH_3$

b. $—CH_2CH_2OH$ —OH $—CH_2Cl$ $—CH{=}CH_2$

PROBLEM 8♦

Tamoxifen slows the growth of some breast tumors by binding to estrogen receptors. Is tamoxifen an *E* or a *Z* isomer?

tamoxifen

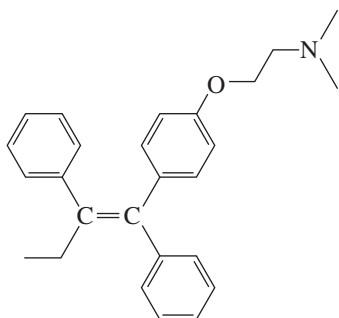
PROBLEM 9

Draw and label the *E* and *Z* isomers for each of the following:

a. $CH_3CH_2CH{=}CHCH_3$

b. $CH_3CH_2C(Cl){=}CHCH_2CH_3$ (Cl on the C bonded to CH_3CH_2)

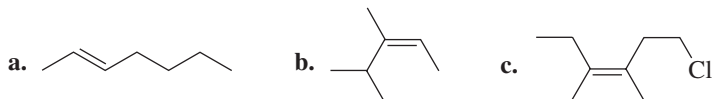
c. $CH_3CH_2C(CH_2CH_2CH_2CH_3){=}C(CH_3CHCH_3)CH_2Cl$ — printed as $CH_3CH_2CH_2CH_2$ above, $CH_3CH_2C{=}CCH_2Cl$, CH_3CHCH_3 below

d. $HOCH_2CH_2C{=}CC{\equiv}CH$ with $O{=}CH$ and $C(CH_3)_3$ below

PROBLEM 10

Draw skeletal structures for each pair of isomers in Problem 9.

PROBLEM 11♦

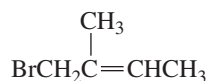
Name each of the following:

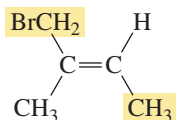
a. **b.** **c.** Cl

PROBLEM-SOLVING STRATEGY

Drawing *E,Z* Structures

Draw the structure of (*E*)-1-bromo-2-methyl-2-butene.

First draw the compound without specifying the isomer so you can see what substituents are bonded to the sp^2 carbons. Then determine the relative priorities of the two groups bonded to each of the sp^2 carbons.

$$\begin{array}{c} \quad CH_3 \\ \quad | \\ BrCH_2C{=}CHCH_3 \end{array}$$

The sp^2 carbon on the left is attached to a CH_3 and a CH_2Br: CH_2Br has the higher priority. The sp^2 carbon on the right is attached to a CH_3 and an H: CH_3 has the higher priority. To draw the *E* isomer, put the two high-priority substituents on opposite sides of the double bond.

$$\begin{array}{ccc} BrCH_2 & & H \\ & C{=}C & \\ CH_3 & & CH_3 \end{array}$$

Now use the strategy you have just learned to solve Problem 12.

PROBLEM 12

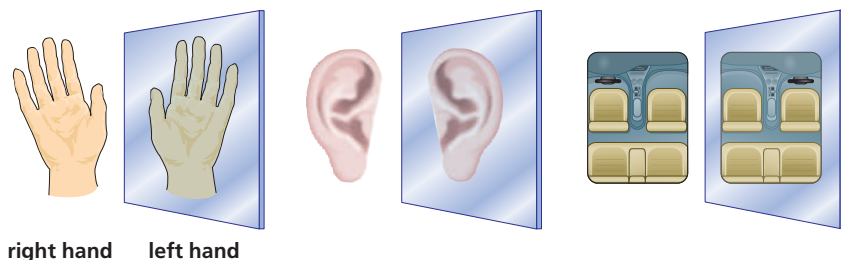
Draw the structure of (*Z*)-2,3-dimethyl-3-heptene.

4.3 A CHIRAL OBJECT HAS A NONSUPERIMPOSABLE MIRROR IMAGE

Why can't you put your right shoe on your left foot? Why can't you put your right glove on your left hand? It is because hands, feet, gloves, and shoes have right-handed and left-handed forms. An object with a right-handed and a left-handed form is said to be **chiral** (ky-ral), a word derived from the Greek word *cheir,* which means "hand."

A chiral object has a *nonsuperimposable mirror image.* In other words, its mirror image *does not look the same* as the object itself. A hand is chiral because when you look at your right hand in a mirror, you see a left hand, not a right hand (Figure 4.2a).

chiral objects

right hand left hand

◀ Figure 4.2a
A chiral object is not the same as its mirror image—they are nonsuperimposable.

A chiral molecule has a nonsuperimposable mirror image.

An achiral molecule has a superimposable mirror image.

In contrast, a chair is not chiral; the reflection of the chair in the mirror looks the same as the chair itself. Objects that are not chiral are said to be **achiral.** An achiral object has a *superimposable mirror image* (Figure 4.2b).

achiral objects

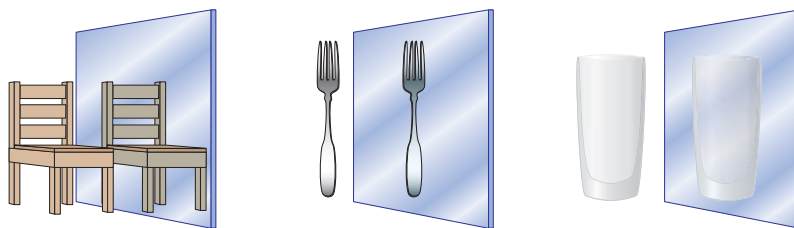



Figure 4.2b
An achiral object is the same as its mirror image—they are superimposable.

PROBLEM 13♦

Which of the following objects are chiral?

a. a wheelbarrow **b.** a shoe **c.** a nail **d.** a screw

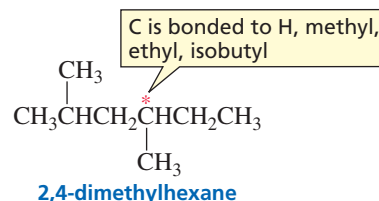
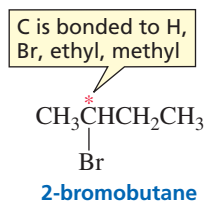
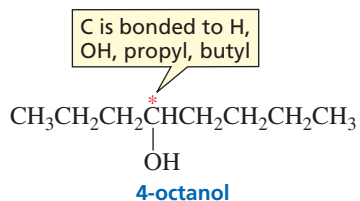
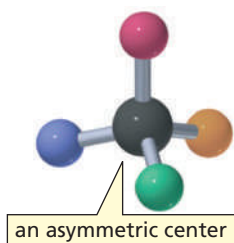
4.4 AN ASYMMETRIC CENTER IS A CAUSE OF CHIRALITY IN A MOLECULE

Objects are not the only things that can be chiral. Molecules can be chiral too. The usual *cause of chirality in a molecule is an asymmetric center*.

An **asymmetric center** (also called a chiral center, a stereogenic center, or a stereocenter) is an atom bonded to four different groups. Each of the following compounds has an asymmetric center that is indicated by a star.

4-octanol

2-bromobutane

2,4-dimethylhexane

A molecule with an asymmetric center is chiral.

PROBLEM 14♦

Which of the following compounds has an asymmetric center?

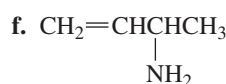
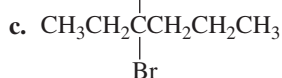
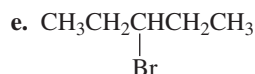
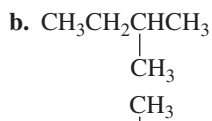
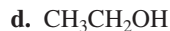
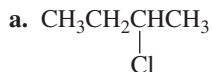
a. $CH_3CH_2CHCH_3$ (with Cl on the CH)

b. $CH_3CH_2CHCH_3$ (with CH_3 on the CH)

c. $CH_3CH_2CCH_2CH_2CH_3$ (with CH_3 and Br on the C)

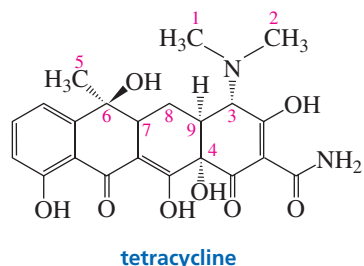
d. CH_3CH_2OH

e. $CH_3CH_2CHCH_2CH_3$ (with Br on the CH)

f. $CH_2{=}CHCHCH_3$ (with NH_2 on the CH)

PROBLEM 15 Solved

Tetracycline is called a broad-spectrum antibiotic because it is active against a wide variety of bacteria. How many asymmetric centers does tetracycline have?

Solution Because an asymmetric center must have four different groups attached to it, only sp^3 carbons can be asymmetric centers. Therefore, we start by locating all the sp^3 carbons in tetracycline. (They are numbered in red.) Tetracycline has nine sp^3 carbons. Four of them (1, 2, 5, and 8) are not asymmetric centers because they are not bonded to four different groups. Tetracycline, therefore, has five asymmetric centers (3, 4, 6, 7, and 9).

tetracycline

4.5 ISOMERS WITH ONE ASYMMETRIC CENTER

A compound with one asymmetric center, such as 2-bromobutane, can exist as two stereoisomers. The two stereoisomers are analogous to a left and a right hand. If we imagine a mirror between the two stereoisomers, we can see they are mirror images of each other. Moreover, they are nonsuperimposable mirror images, which makes them different molecules.

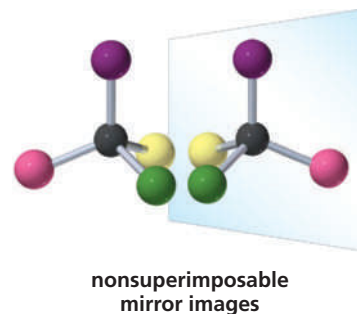
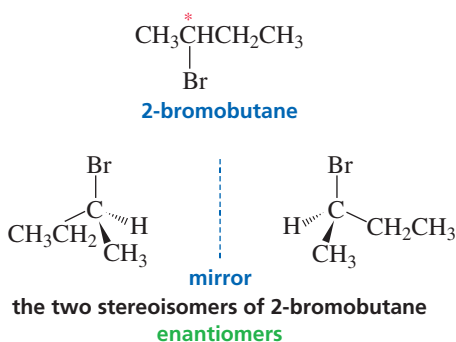
$CH_3\overset{*}{C}HCH_2CH_3$ (with Br on the starred carbon)

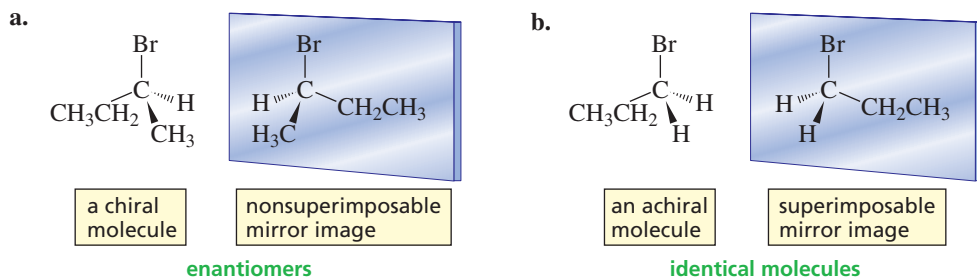
2-bromobutane

mirror

the two stereoisomers of 2-bromobutane

enantiomers

nonsuperimposable mirror images

Molecules that are nonsuperimposable mirror images of each other are called **enantiomers** (from the Greek *enantion*, which means "opposite"). Thus, the two stereoisomers of 2-bromobutane are enantiomers.

A molecule that has a *nonsuperimposable* mirror image, like an object that has a *nonsuperimposable* mirror image, is *chiral* (Figure 4.3a). Therefore, each member of a pair of enantiomers is chiral. A molecule that has a *superimposable* mirror image, like an object that has a *superimposable* mirror image, is *achiral* (Figure 4.3b). Notice that chirality is a property of an entire object or an entire molecule.

◀ **Figure 4.3**
(a) A chiral molecule has a nonsuperimposable mirror image.
(b) An achiral molecule has a superimposable mirror image. To see that the achiral molecule is superimposable on its mirror image, mentally rotate the molecule clockwise.

PROBLEM 16♦

Which of the compounds in Problem 14 can exist as enantiomers?

4.6 HOW TO DRAW ENANTIOMERS

A solid wedge represents a bond that extends out of the plane of the paper toward the viewer.

A hatched wedge represents a bond that points back from the plane of the paper away from the viewer.

When you draw a perspective formula, make sure that the two bonds in the plane of the paper are adjacent to one another; neither the solid wedge nor the hatched wedge should be drawn between them.

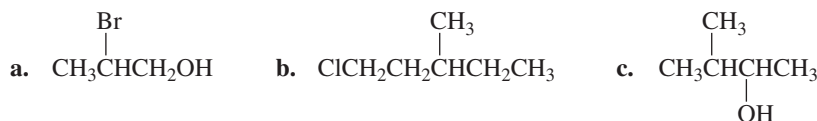
Chemists generally draw enantiomers using *perspective formulas*. A **perspective formula** shows two of the bonds to the asymmetric center in the plane of the paper, one bond as a solid wedge protruding forward out of the paper, and the fourth bond as a hatched wedge extending behind the paper. The solid wedge and the hatched wedge must be adjacent to one another. When you draw the first enantiomer, the four groups bonded to the asymmetric center can be placed around it in any order. You can then draw the second enantiomer by drawing the mirror image of the first enantiomer.

Br, H, C, CH_3, CH_2CH_3 — Br, H_3C, C, H, CH_3CH_2

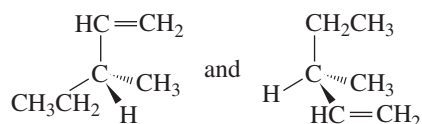
perspective formulas of the enantiomers of 2-bromobutane

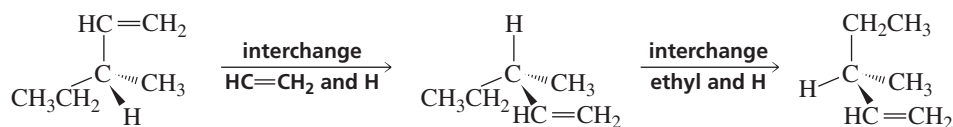
PROBLEM 17

Draw enantiomers for each of the following using perspective formulas:

a. $CH_3CH(Br)CH_2OH$ **b.** $ClCH_2CH_2CH(CH_3)CH_2CH_3$ **c.** $CH_3CH(CH_3)CH(OH)CH_3$

PROBLEM 18 Solved

Do the following structures represent identical compounds or a pair of enantiomers?

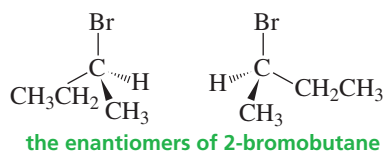
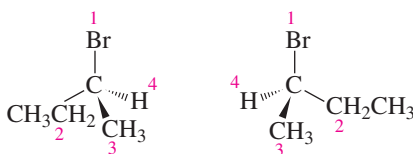
$HC{=}CH_2$, C, CH_3, CH_3CH_2, H and CH_2CH_3, H, C, CH_3, $HC{=}CH_2$

Solution Interchanging two atoms or groups attached to an asymmetric center produces an enantiomer. Interchanging two atoms or groups a second time brings you back to the original compound. Because groups have to be interchanged twice to get from one structure to the other, the two structures represent identical compounds.

$HC{=}CH_2$, C, CH_3, CH_3CH_2, H → **interchange $HC{=}CH_2$ and H** → H, C, CH_3, CH_3CH_2, $HC{=}CH_2$ → **interchange ethyl and H** → CH_2CH_3, H, C, CH_3, $HC{=}CH_2$

In Section 4.7, you will learn another way to determine if two structures represent identical compounds or enantiomers.

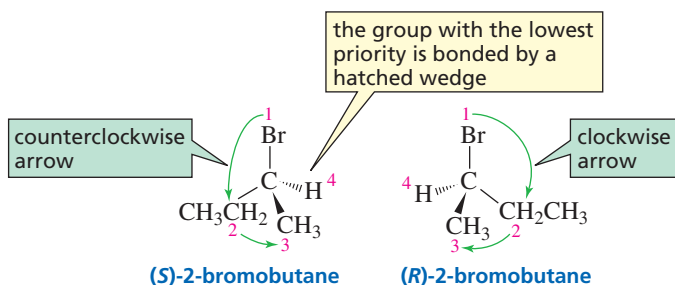
4.7 NAMING ENANTIOMERS BY THE *R,S* SYSTEM

How do we name the different stereoisomers of a compound like 2-bromobutane so that we know which one we are talking about? We need a system of nomenclature that indicates the arrangement of the atoms or groups around the asymmetric center. Chemists use the letters *R* and *S* for this purpose. For any pair of enantiomers with one asymmetric center, one member will have the *R* **configuration** and the other will have the *S* **configuration.**

First, let's look at how to determine the configuration of the enantiomers of 2-bromobutane as an example.

the enantiomers of 2-bromobutane

1. **Rank the groups (or atoms) bonded to the asymmetric center in order of priority.** The atomic numbers of the atoms directly attached to the asymmetric center determine the relative priorities. The higher the *atomic* number of the atom, the higher the priority. (This should remind you of the way that relative priorities are determined for the *E,Z* system because the priorities were originally devised for the *R,S* system and later adopted for the *E,Z* system.) Therefore, bromine has the highest priority (1), the ethyl group has the second highest priority (2), the methyl group has the third highest priority (3), and hydrogen has the lowest priority (4). (Revisit Section 4.2 if you do not understand how these priorities are assigned.)

The greater the atomic number of the atom directly attached to the asymmetric center, the higher the priority of the substituent.

If the atoms attached to the asymmetric center are the same, the atoms attached to those atoms are compared.

2. ***If the group (or atom) with the lowest priority (4) is bonded by a hatched wedge,*** draw an arrow from the group (or atom) with the highest priority (1) to the one with the second highest priority (2), and then to the one with the third highest priority (3). If the arrow points clockwise, the compound has the *R* configuration (*R* is for *rectus*, which is Latin for "right"). If the arrow points counterclockwise, then the compound has the *S* configuration (*S* is for *sinister*, which is Latin for "left"). The letter *R* or *S* (in parentheses) precedes the systematic name of the compound.

Clockwise specifies *R* if the lowest priority substituent is on a hatched wedge.

Counterclockwise specifies *S* if the lowest priority substituent is on a hatched wedge.

the group with the lowest priority is bonded by a hatched wedge

counterclockwise arrow

clockwise arrow

(*S*)-2-bromobutane (*R*)-2-bromobutane

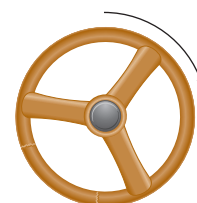
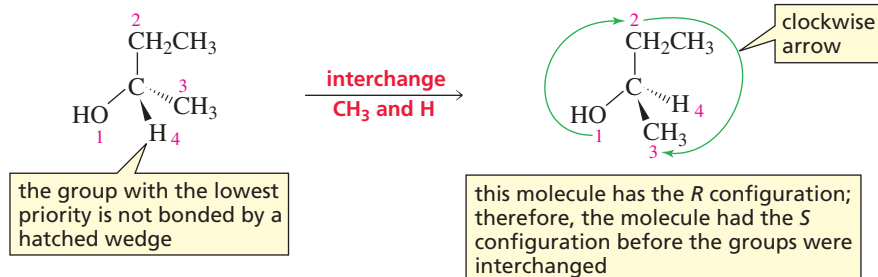
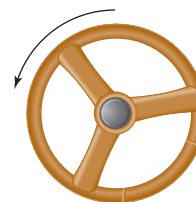
right turn

3. ***If the group (or atom) with the lowest priority (4) is not bonded by a hatched wedge,*** then interchange group 4 with the group that is bonded by a hatched wedge. Then proceed as in step 2—namely, draw an arrow from (1) to (2) to (3). Since the arrow points clockwise, the compound with the interchanged groups has the *R* configuration. Therefore, the original compound, before the groups were interchanged, has the *S* configuration; see problem 18.

interchange CH_3 and H

the group with the lowest priority is not bonded by a hatched wedge

clockwise arrow

this molecule has the *R* configuration; therefore, the molecule had the *S* configuration before the groups were interchanged

left turn

If you forget which direction corresponds to which configuration, imagine driving a car and turning the steering wheel clockwise to make a right turn or turning it counterclockwise to make a left turn.

PROBLEM 19♦

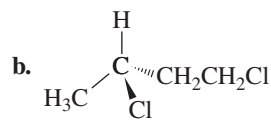
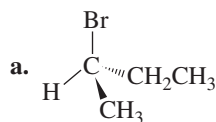
Assign relative priorities to the groups or atoms in each of the following sets:

a. $-CH_2OH$ $-CH_3$ $-H$ $-CH_2CH_2OH$
b. $-CH_2Br$ $-OH$ $-CH_3$ $-CH_2OH$
c. $-CH(CH_3)_2$ $-CH_2CH_2Br$ $-Cl$ $-CH_2CH_2CH_2Br$

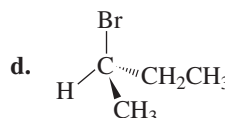
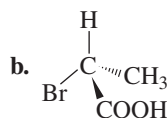
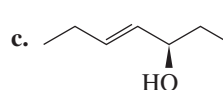
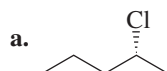
PROBLEM 20♦

Name the following:

a. Br, H, CH_2CH_3, CH_3 on C

b. H, H_3C, CH_2CH_2Cl, Cl on C

PROBLEM 21♦ Solved

Do the following compounds have the *R* or the *S* configuration?

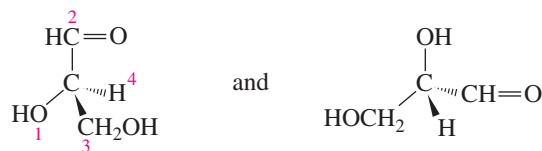
a. Cl
b. H, Br, CH_3, COOH on C
c. HO
d. Br, H, CH_2CH_3, CH_3 on C

Solution to 21a Start by adding the missing solid wedge and the H to which it is bonded. The solid wedge can be drawn either to the right or to the left of the hatched wedge. (Recall that the solid and hatched wedges must be adjacent.)

Because the group with the lowest priority is not on the hatched wedge, interchange the Cl and H so that H is on the hatched wedge. An arrow drawn from (1) to (2) to (3) indicates that the compound has the *S* configuration. Therefore, the compound before the pair was interchanged had the *R* configuration.

PROBLEM-SOLVING STRATEGY

Recognizing Pairs of Enantiomers

Do the structures represent identical compounds or a pair of enantiomers?

HC=O (2), HO (1), H (4), CH_2OH (3) on C   and   OH, $HOCH_2$, CH=O, H on C

The easiest way to answer this question is to determine their configurations. If one has the *R* configuration and the other has the *S* configuration, then they are enantiomers. If they both have the *R* configuration or they both have the *S* configuration, then they are identical compounds.

The OH group has the highest priority, the H has the lowest priority, and the Cs of the other two groups tie. The CH=O group has a higher priority than the CH_2OH group, because if an atom is doubly bonded to another atom, the priority system treats it as if it were singly bonded to two of those atoms. Thus, the C of the CH=O group is considered to be bonded to O, O, H, whereas the C of the CH_2OH group is considered to be bonded to O, H, H. An O cancels in each group, leaving O, H in the CH=O group and H, H in the CH_2OH group.

Because the structure on the left has the *R* configuration and the structure on the right has the *S* configuration, these two structures represent a pair of enantiomers.

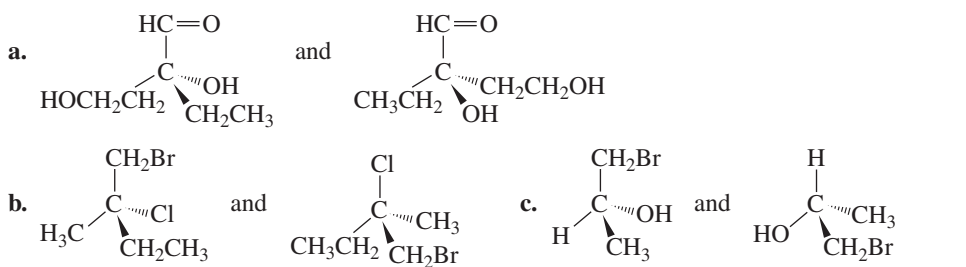
Now use the strategy you have just learned to solve Problem 22.

PROBLEM 22♦

Do the following structures represent identical compounds or a pair of enantiomers?

a. HC=O / C with $HOCH_2CH_2$, OH (hatched), CH_2CH_3 (wedge) and HC=O / C with CH_3CH_2, CH_2CH_2OH (hatched), OH (wedge)

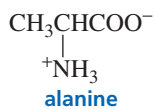
b. CH_2Br / C with H_3C, Cl (hatched), CH_2CH_3 (wedge) and Cl / C with CH_3CH_2, CH_3 (hatched), CH_2Br (wedge)

c. CH_2Br / C with H, OH (hatched), CH_3 (wedge) and H / C with HO, CH_3 (hatched), CH_2Br (wedge)

PROBLEM-SOLVING STRATEGY

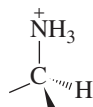
Drawing an Enantiomer with a Desired Configuration

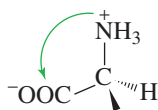
(*S*)-Alanine is a naturally occurring amino acid. Draw its structure using a perspective formula.

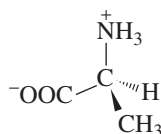
$$CH_3CH(\overset{+}{N}H_3)COO^-$$

alanine

First draw the bonds about the asymmetric center. (Remember that the solid wedge and the hatched wedge must be adjacent to one another.)

Put the group with the lowest priority on the hatched wedge. Put the group with the highest priority on any remaining bond.

$\overset{+}{N}H_3$ / C, H (hatched)

Because you have been asked to draw the *S* enantiomer, draw an arrow counterclockwise from the group with the highest priority to the next available bond and put the group with the second highest priority on that bond.

$\overset{+}{N}H_3$ / C with ^-OOC, H (hatched)

Put the remaining substituent (the one with the third highest priority) on the last available bond.

$\overset{+}{N}H_3$ / C with ^-OOC, H (hatched), CH_3 (wedge)

Now use the strategy you have just learned to solve Problem 23.

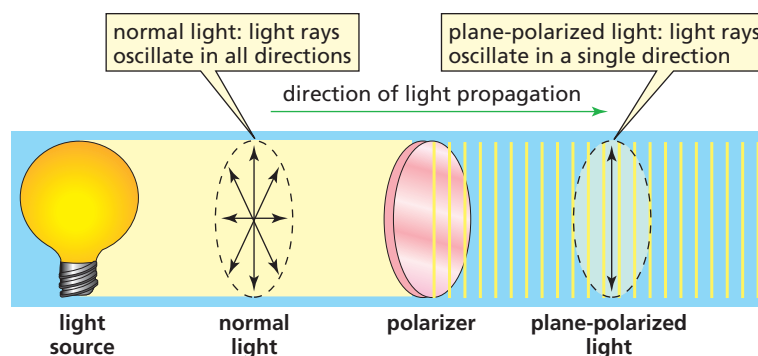
PROBLEM 23

Draw a perspective formula for each of the following:

a. (*S*)-2-chlorobutane **b.** (*R*)-1,2-dibromobutane

4.8 CHIRAL COMPOUNDS ARE OPTICALLY ACTIVE

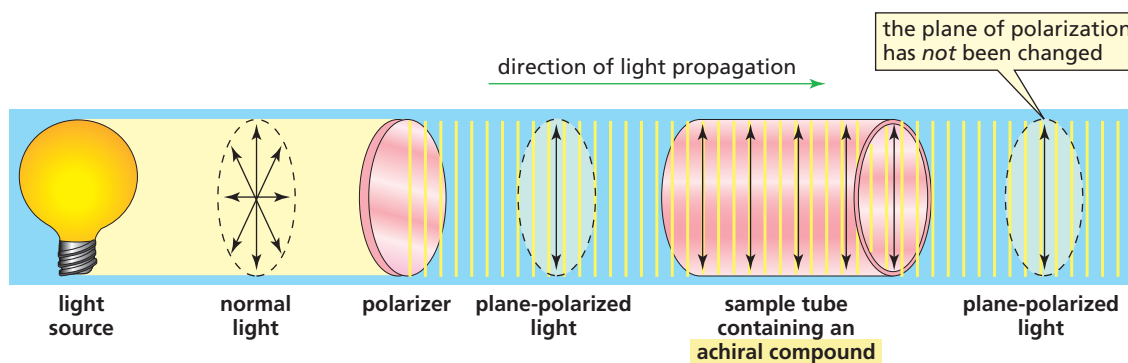
Enantiomers share many of the same properties, including the same boiling points, the same melting points, and the same solubilities. In fact, all the physical properties of enantiomers are the same except those that stem from how groups bonded to the asymmetric center are arranged in space. One property that enantiomers do not share is the way they interact with plane-polarized light.

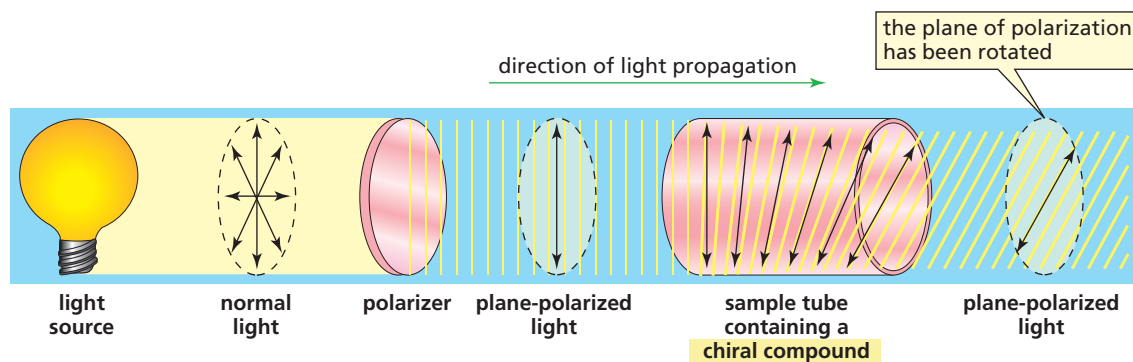
Normal light, such as that coming from a light bulb or the sun, consists of rays that oscillate in all directions. In contrast, all the rays in a beam of **plane-polarized light** oscillate in a single plane. Plane-polarized light is produced by passing normal light through a polarizer (Figure 4.4).

▲ **Figure 4.4**
Only light oscillating in a single plane can pass through a polarizer.

When light is filtered through two polarizers (polarized lenses) at a 90 ° angle to one another, none of the light passes through.

You can experience the effect of a polarizer by wearing a pair of polarized sunglasses. Polarized sunglasses allow only light oscillating in a single plane to pass through, which is why they block reflections (glare) more effectively than nonpolarized sunglasses do.

In 1815, the physicist Jean-Baptiste Biot discovered that certain naturally occurring organic compounds are able to rotate the **plane of polarization** of plane-polarized light. He noted that some compounds rotated it clockwise and some rotated it counterclockwise. He proposed that the ability to rotate the plane of polarization of plane-polarized light was due to some asymmetry in the molecules. It was later determined that the asymmetry was associated with compounds having one or more asymmetric centers.

When plane-polarized light passes through a solution of achiral molecules, the light emerges from the solution with its plane of polarization unchanged (Figure 4.5).

▲ **Figure 4.5**
An achiral compound does not rotate the plane of polarization of plane-polarized light.

On the other hand, when plane-polarized light passes through a solution of chiral molecules, the light emerges with its plane of polarization rotated either clockwise or counterclockwise (Figure 4.6). If one enantiomer rotates it clockwise, its mirror image will rotate it exactly the same amount counterclockwise.

▲ **Figure 4.6**
A chiral compound rotates the plane of polarization of plane-polarized light.

An achiral compound does not rotate the plane of polarization of plane-polarized light.

A chiral compound rotates the plane of polarization of plane-polarized light.

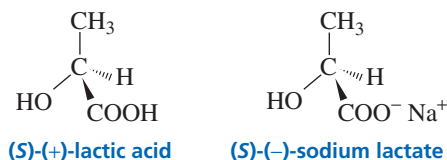
A compound that rotates the plane of polarization of plane-polarized light is said to be **optically active.** In other words, chiral compounds are optically active, and achiral compounds are **optically inactive.**

If an optically active compound rotates the plane of polarization clockwise, then the compound is said to be **dextrorotatory,** which can be indicated in the compound's name by the prefix (+). If it rotates the plane of polarization counterclockwise, then it is said to be **levorotatory,** which can be indicated by (−).

Do not confuse (+) and (−) with *R* and *S*. The (+) and (−) symbols indicate the direction in which an optically active compound rotates the plane of polarization of plane-polarized light, whereas *R* and *S* indicate the arrangement of the groups about an asymmetric center. Some compounds with the *R* configuration are (+) and some are (−). Likewise, some compounds with the *S* configuration are (+) and some are (−).

For example, (*S*)-lactic acid and (*S*)-sodium lactate both have an *S* configuration, but (*S*)-lactic acid is dextrorotatory whereas (*S*)-sodium lactate is levorotatory. When we know which direction an optically active compound rotates the plane of polarization, we can incorporate (+) or (−) into its name.

CH_3, HO, C, H, COOH — **(*S*)-(+)-lactic acid**

CH_3, HO, C, H, COO^- Na^+ — **(*S*)-(−)-sodium lactate**

We can tell by looking at the structure of a compound whether it has the *R* or the *S* configuration, but the only way we can tell whether a compound is dextrorotatory (+) or levorotatory (−) is to put the compound in a polarimeter. This is an instrument that measures the direction and the amount the plane of polarization of plane-polarized light is rotated.

PROBLEM 24♦

a. Is (*R*)-lactic acid dextrorotatory or levorotatory?
b. Is (*R*)-sodium lactate dextrorotatory or levorotatory?

PROBLEM 25♦ Solved

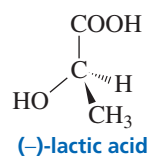
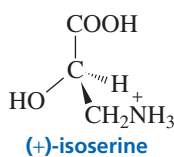
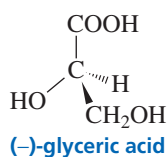
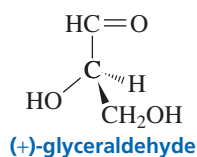
What is the configuration of the following compounds?

a. (−)-glyceraldehyde **b.** (−)-glyceric acid **c.** (+)-isoserine **d.** (+)-lactic acid

HC=O, HO, C, H, CH_2OH — **(+)-glyceraldehyde**

COOH, HO, C, H, CH_2OH — **(−)-glyceric acid**

COOH, HO, C, H, $CH_2\overset{+}{N}H_3$ — **(+)-isoserine**

COOH, HO, C, H, CH_3 — **(−)-lactic acid**

Solution to 25a We know that (+)-glyceraldehyde has the *R* configuration because the group with the lowest priority is on the hatched wedge and the arrow drawn from the OH group to the HC=O group is clockwise. Therefore, (−)-glyceraldehyde has the *S* configuration.

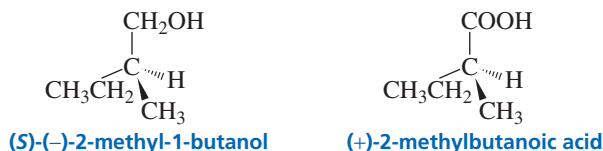
PROBLEM 26 Solved

(*S*)-(−)-2-Methyl-1-butanol can be converted to (+)-2-methylbutanoic acid without breaking any of the bonds to the asymmetric center. What is the configuration of (−)-2-methylbutanoic acid?

CH_2OH, C, H, CH_3CH_2, CH_3

(*S*)-(−)-2-methyl-1-butanol

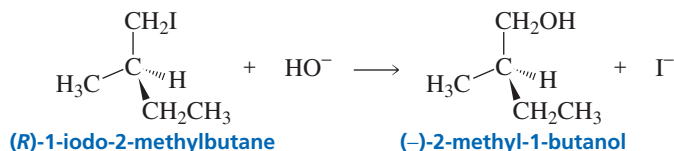
COOH, C, H, CH_3CH_2, CH_3

(+)-2-methylbutanoic acid

Solution We know that (+)-2-methylbutanoic acid has the configuration shown here because it was formed from (*S*)-(−)-2-methyl-1-butanol without breaking any bonds to the asymmetric center. From its structure, we can determine that (+)-2-methylbutanoic acid has the *S* configuration. Therefore, (−)-2-methylbutanoic acid has the *R* configuration.

PROBLEM 27♦

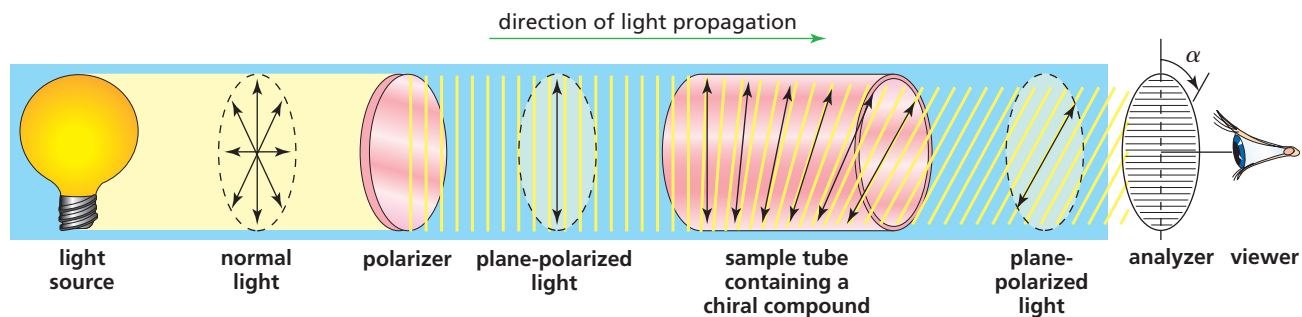
The reaction of (*R*)-1-iodo-2-methylbutane with hydroxide ion forms an alcohol without breaking any bonds to the asymmetric center. The alcohol rotates the plane of polarization of plane-polarized light counterclockwise. What is the configuration of (+)-2-methyl-1-butanol?

CH_2I, C, H, H_3C, CH_2CH_3 + HO^- ⟶ CH_2OH, C, H, H_3C, CH_2CH_3 + I^-

(*R*)-1-iodo-2-methylbutane **(−)-2-methyl-1-butanol**

4.9 HOW SPECIFIC ROTATION IS MEASURED

The direction and amount an optically active compound rotates the plane of polarization of plane-polarized light can be measured with an instrument called a **polarimeter.** Figure 4.7 provides a simplified description of how a polarimeter functions.

In a polarimeter, monochromatic (single-wavelength) light passes through a polarized lens and emerges as plane-polarized light, which then passes through a sample tube. If the tube is empty, the light emerges from it with its plane of polarization unchanged. The light then passes through an analyzer, which is a second polarized lens mounted on an eyepiece with a dial marked in degrees. The user looks through the eyepiece and rotates the analyzer until he or she sees total darkness. At this point the analyzer is at a right angle to the polarizer, so no light passes through. This analyzer setting corresponds to zero rotation.

The sample to be measured is then placed in the sample tube. If the sample is optically active, it will rotate the plane of polarization. The analyzer, therefore, will no longer block all the light, so some light will reach the user's eye. The user now rotates the analyzer again until no light passes through. The amount the analyzer is rotated can be read from the dial. This value, which is measured in degrees, is called the **observed rotation** (α) (Figure 4.7).

▲ **Figure 4.7**
A schematic drawing of a polarimeter.

Each optically active compound has a characteristic specific rotation. A compound's **specific rotation** is the rotation caused by a pure liquid or by a solution of 1.0 g of the compound per 100 mL of solution in a sample tube 1.0 dm long at a specified temperature and wavelength.* The specific rotation can be calculated from the observed rotation using the following formula,

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \times c}$$

where $[\alpha]$ is the specific rotation, T is temperature in degrees Celsius, λ is the wavelength of the incident light (when the sodium D-line is used, λ is indicated as D), α is the observed rotation, l is the length of the sample tube in decimeters, and c is the concentration of the sample in grams per 100 mL of solution.

If one enantiomer has a specific rotation of +5.75, the specific rotation of the other enantiomer must be −5.75, because the mirror-image molecule rotates the plane of polarization the same amount but in the opposite direction. The specific rotations of some common compounds are listed in Table 4.1.

CH_2OH / CH_3—C—H / CH_2CH_3

(R)-2-methyl-1-butanol

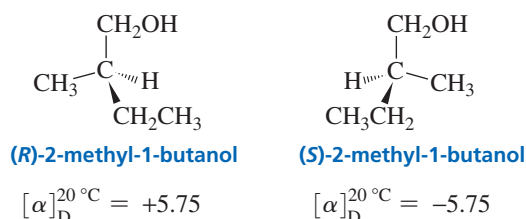
$[\alpha]_D^{20\,°C} = +5.75$

CH_2OH / H—C—CH_3 / CH_3CH_2

(S)-2-methyl-1-butanol

$[\alpha]_D^{20\,°C} = -5.75$

Table 4.1 Specific Rotation of Some Naturally Occurring Compounds

Compound	Specific rotation
Cholesterol	−31.5
Cocaine	−16
Codeine	−136
Morphine	−132
Penicillin V	+233
Progesterone	+172
Sucrose (table sugar)	+66.5
Testosterone	+109

A mixture of equal amounts of two enantiomers—such as (*R*)-(−)-lactic acid and (*S*)-(+)-lactic acid—is called a **racemic mixture** or a **racemate.** Racemic mixtures are optically inactive because for every molecule in a racemic mixture that rotates the plane of polarization in one direction, there is a mirror-image molecule that rotates the plane in the opposite direction. As a result, the light emerges from a racemic mixture with its plane of polarization unchanged. The symbol (±) is used to specify a racemic mixture. Thus, (±)-2-bromobutane indicates a mixture of 50% (+)-2-bromobutane and 50% (−)-2-bromobutane.

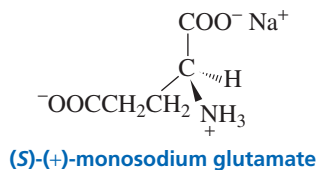
PROBLEM 28♦

A solution containing one gram of a compound dissolved in 100 mL of a solvent was found to have an observed rotation of +13.4°. What is the specific rotation of the compound?

PROBLEM 29♦

(*S*)-(+)-Monosodium glutamate (MSG) is a flavor enhancer used in many foods. Some people have an allergic reaction to MSG (including headache, chest pain, and an overall feeling of weakness). "Fast food" often contains substantial amounts of MSG, which is widely used in Chinese food as well. (*S*)-(+)-MSG has a specific rotation of +24.

$COO^- Na^+$ / C—H / $^-OOCCH_2CH_2$ / $\overset{+}{N}H_3$

(S)-(+)-monosodium glutamate

a. What is the specific rotation of (*R*)-(−)-monosodium glutamate?
b. What is the specific rotation of a racemic mixture of MSG?

*Unlike observed rotation, which is measured in degrees, specific rotation has units of 10^{-1} deg cm^2 g^{-1}. In this book, values of specific rotation will be given without units.

PROBLEM 30♦

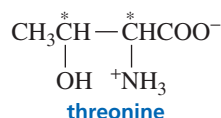
Naproxen, a nonsteroidal anti-inflammatory drug that is the active ingredient in Aleve, has a specific rotation of +66. Does naproxen have the *R* or the *S* configuration?

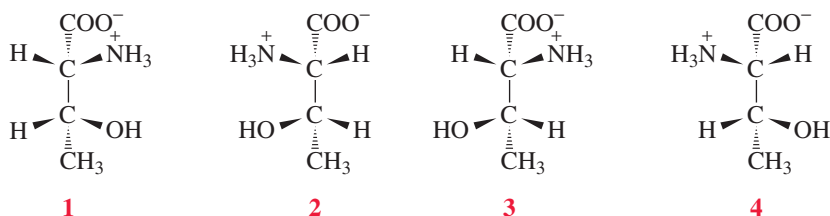
4.10 ISOMERS WITH MORE THAN ONE ASYMMETRIC CENTER

Many organic compounds have more than one asymmetric center. The more asymmetric centers a compound has, the more stereoisomers it can have. If we know the number of asymmetric centers, we can calculate the maximum number of stereoisomers for that compound: *a compound can have a maximum of* 2^n *stereoisomers, where* n *equals the number of asymmetric centers.* For example, the amino acid threonine has two asymmetric centers. Therefore, it can have a maximum of four ($2^2 = 4$) stereoisomers.

$$CH_3\overset{*}{C}H(OH)-\overset{*}{C}H(\overset{+}{N}H_3)COO^-$$

threonine

Diastereomers are stereoisomers that are not enantiomers.

The four stereoisomers of threonine consist of two pairs of enantiomers. Stereoisomers **1** and **2** are nonsuperimposable mirror images. They, therefore, are enantiomers. Stereoisomers **3** and **4** are also enantiomers. Stereoisomers **1** and **3** are not identical, and they are not mirror images. Such stereoisomers are called **diastereomers.** *Diastereomers are stereoisomers that are not enantiomers*. Stereoisomers **1** and **4**, **2** and **3**, and **2** and **4** are also pairs of diastereomers. Notice that the configuration of one of the asymmetric centers is the same in both of a pair of diastereomers, but the configuration of the other asymmetric center is different.

1	2	3	4
COO^-; H, $\overset{+}{N}H_3$ on C; H, OH on C; CH_3	COO^-; $H_3\overset{+}{N}$, H on C; HO, H on C; CH_3	COO^-; H, $\overset{+}{N}H_3$ on C; HO, H on C; CH_3	COO^-; $H_3\overset{+}{N}$, H on C; H, OH on C; CH_3

Enantiomers have *identical physical properties* (except for the way they interact with polarized light) and *identical chemical properties*, so they react at the same rate with an achiral reagent. Diastereomers have *different physical properties*, meaning different melting points, different boiling points, different solubilities, different specific rotations, and so on, and *different chemical properties*, so they react with an achiral reagent at different rates.

PROBLEM 31♦

a. Stereoisomers with two asymmetric centers are called _____ if the configuration of both asymmetric centers in one stereoisomer is the opposite of the configuration of the asymmetric centers in the other stereoisomer.
b. Stereoisomers with two asymmetric centers are called _____ if the configuration of both asymmetric centers in one stereoisomer is the same as the configuration of the asymmetric centers in the other stereoisomer.
c. Stereoisomers with two asymmetric centers are called _____ if one of the asymmetric centers has the same configuration in both stereoisomers and the other asymmetric center has the opposite configuration in the two stereoisomers.

PROBLEM 32♦

a. How many asymmetric centers does cholesterol have?
b. What is the maximum number of stereoisomers that cholesterol can have? (Only one of these is found in nature.)

cholesterol

PROBLEM 33

Draw the stereoisomers of the following amino acids. Indicate pairs of enantiomers and pairs of diastereomers.

a. $CH_3CHCH_2—CHCOO^-$ with CH_3 and $^+NH_3$ substituents — leucine

b. $CH_3CH_2CH—CHCOO^-$ with CH_3 and $^+NH_3$ substituents — isoleucine

4.11 STEREOISOMERS OF CYCLIC COMPOUNDS

1-Bromo-2-methylcyclopentane also has two asymmetric centers and four stereoisomers. Because the compound is cyclic, the substituents can be either cis or trans (Section 3.13). Enantiomers can be drawn for both the cis isomer and for the trans isomer. Each of the four stereoisomers is chiral.

cis-1-bromo-2-methylcyclopentane
enantiomers

trans-1-bromo-2-methylcyclopentane
enantiomers

1-Bromo-3-methylcyclohexane also has two asymmetric centers. The carbon that is bonded to a Br and an H is also bonded to two different carbon-containing groups (—$CH_2CH(CH_3)CH_2CH_2CH_2$— and —$CH_2CH_2CH_2CH(CH_3)CH_2$—), so it is an asymmetric center. The carbon that is bonded to a CH_3 and a H is also bonded to two different carbon-containing groups, so it too is an asymmetric center.

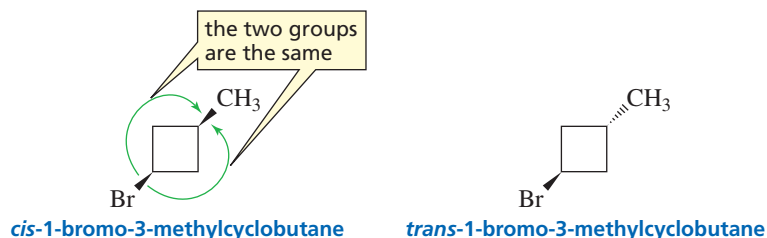
these two groups are different
asymmetric center
asymmetric center

Because the compound has two asymmetric centers, it has four stereoisomers. Enantiomers can be drawn for both the cis isomer and for the trans isomer. Each of the four stereoisomers is chiral.

cis-1-bromo-3-methylcyclohexane
enantiomers

trans-1-bromo-3-methylcyclohexane
enantiomers

1-Bromo-3-methylcyclobutane does not have any asymmetric centers. The C-1 carbon has a Br and an H attached to it, but its other two groups [$—CH_2CH(CH_3)CH_2—$] are identical; C-3 has a CH_3 and a H attached to it, but its other two groups [$—CH_2CH(Br)CH_2—$] are identical. Because the compound does not have a carbon with four different groups attached to it, it has only two stereoisomers, the cis isomer and the trans isomer. Both stereoisomers are achiral.

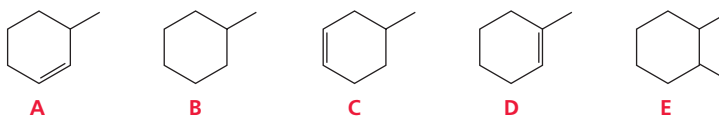
cis-1-bromo-3-methylcyclobutane *trans*-1-bromo-3-methylcyclobutane

1-Bromo-4-methylcyclohexane also has no asymmetric centers. Therefore, the compound has only two stereoisomers, the cis isomer and the trans isomer. Both stereoisomers are achiral.

Br–⬡–CH_3 Br–⬡–CH_3

cis-1-bromo-4-methylcyclohexane *trans*-1-bromo-4-methylcyclohexane

PROBLEM 34♦

Which of the following compounds has one or more asymmetric centers?

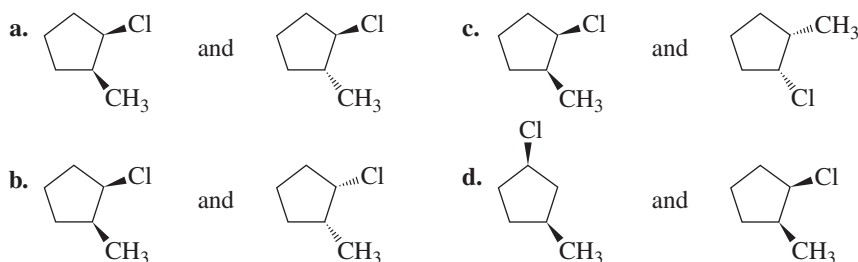
A B C D E

PROBLEM 35♦ Solved

Indicate whether the following pairs of compounds are identical or are enantiomers, diastereomers, or constitutional isomers:

a. Cl, CH_3 and Cl, CH_3

b. Cl, CH_3 and Cl, CH_3

c. Cl, CH_3 and CH_3, Cl

d. Cl, CH_3 and Cl, CH_3

Solution to 35a The configuration of one of the asymmetric centers (the one bonded to Cl) is the same in both compounds; the configuration of the other asymmetric center (the one bonded to CH_3) is different in the two compounds. The two compounds, therefore, are diastereomers.

PROBLEM 36

a. Draw the stereoisomers of 2-bromo-3-chloropentane.
b. Draw the stereoisomers of 1-bromo-2-chlorocyclopentane.

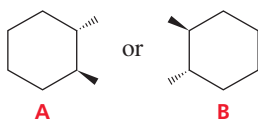
PROBLEM-SOLVING STRATEGY

Drawing Enantiomers and Diastereomers

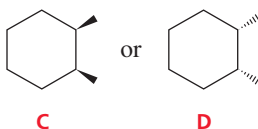
Draw an enantiomer and a diastereomer for the following compound:

You can draw an enantiomer in one of two ways. You can change the configuration of all the asymmetric centers by changing all wedges to dashes and all dashes to wedges as in **A.** Or you can draw a mirror image of the compound as in **B.** Notice that since **A** and **B** are each an enantiomer of the given compound, **A** and **B** are identical. (You can see they are identical if you rotate **B** 180° clockwise.)

or

A B

You can draw a diastereomer by changing the configuration of only one of the asymmetric centers as in **C** or **D**.

or

C D

Now use the strategy you have just learned to solve Problem 37.

PROBLEM 37

Draw a diastereomer for each of the following compounds:

a. CH_3 H C OH Br C H CH_3

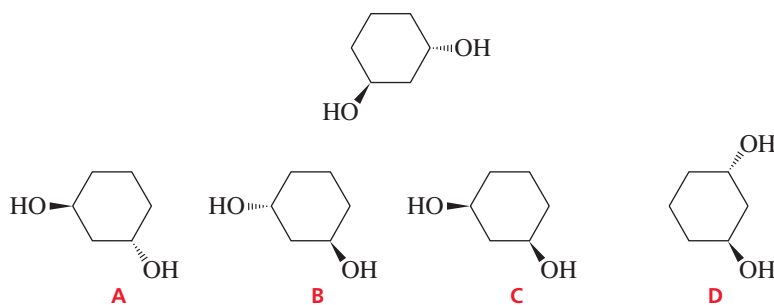
b. HO CH_3

PROBLEM 38♦

Indicate whether each of the structures in the second row is an enantiomer of, is a diastereomer of, or is identical to the structure in the top row.

OH HO

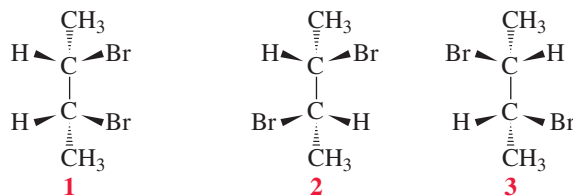
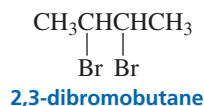
HO OH HO OH HO OH OH OH

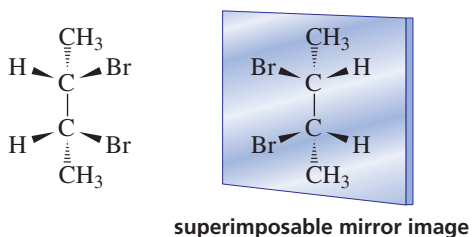
A B C D

4.12 MESO COMPOUNDS HAVE ASYMMETRIC CENTERS BUT ARE OPTICALLY INACTIVE

In the examples we have just seen, the compounds with two asymmetric centers had four stereoisomers. However, some compounds with two asymmetric centers have only three stereoisomers. This is why we emphasized in Section 4.10 that the *maximum* number of stereoisomers a compound with n asymmetric centers can have is 2^n, instead of stating that a compound with n asymmetric centers has 2^n stereoisomers.

An example of a compound with two asymmetric centers that has only three stereoisomers is 2,3-dibromobutane.

$$\underset{\displaystyle\ \ \ \ \ \ \ \ \ \ \ \ \text{Br}\ \ \text{Br}}{CH_3CHCHCH_3}$$

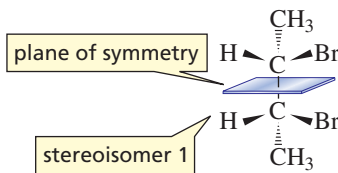
2,3-dibromobutane

The "missing" isomer is the mirror image of **1**, because **1** and its mirror image are the same molecule. You can see that **1** and its mirror image are identical if you rotate the mirror image 180°.

superimposable mirror image

A meso compound is achiral.

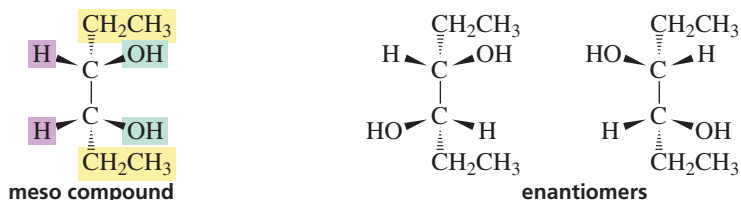
Stereoisomer **1** is called a *meso compound*. Even though a meso (mee-zo) compound has asymmetric centers, it is achiral. A meso compound does not rotate plane-polarized light because it is superimposable on its mirror image.

A **meso compound** can be recognized by the fact that it has two (or more) asymmetric centers and a plane of symmetry. A **plane of symmetry** cuts the molecule in half so that one half is the mirror image of the other. A molecule with a plane of symmetry does not have an enantiomer; it is achiral. Compare stereoisomer **1**, which has a plane of symmetry and thus no enantiomer, with stereoisomer **2**, which does not have a plane of symmetry and therefore *does* have an enantiomer.

A meso compound has two or more asymmetric centers and a plane of symmetry.

If a compound has a plane of symmetry, it is achiral (that is, not optically active) even though it has asymmetric centers.

It is easy to recognize when a compound with two asymmetric centers has a stereoisomer that is a meso compound—the four atoms or groups bonded to one asymmetric center are identical to the four atoms or groups bonded to the other asymmetric center. *A compound with the same four atoms or groups bonded to two different asymmetric centers will have three stereoisomers: one will be a meso compound, and the other two will be enantiomers.*

If a compound with two asymmetric centers has the same four groups bonded to each of the asymmetric centers, one of its stereoisomers will be a meso compound.

meso compound **enantiomers**

Tartaric acid has three stereoisomers because each of its two asymmetric centers has the same set of four substituents.

COOH
H ◀ C ◀ OH
H ◀ C ◀ OH
COOH
meso compound

COOH
H ◀ C ◀ OH
HO ◀ C ◀ H
COOH

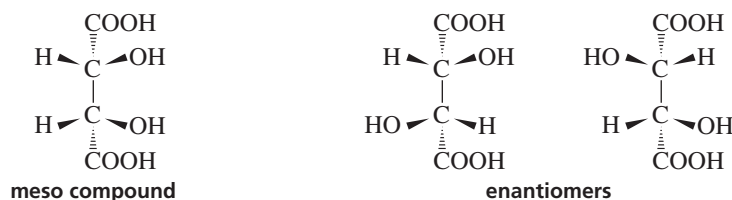
COOH
HO ◀ C ◀ H
H ◀ C ◀ OH
COOH
enantiomers

The physical properties of the three stereoisomers of tartaric acid are listed in Table 4.2. The meso compound and either of the enantiomers are diastereomers. Notice that the physical properties of the enantiomers are the same, whereas the physical properties of the diastereomers are different.

Table 4.2 Physical Properties of the Stereoisomers of Tartaric Acid

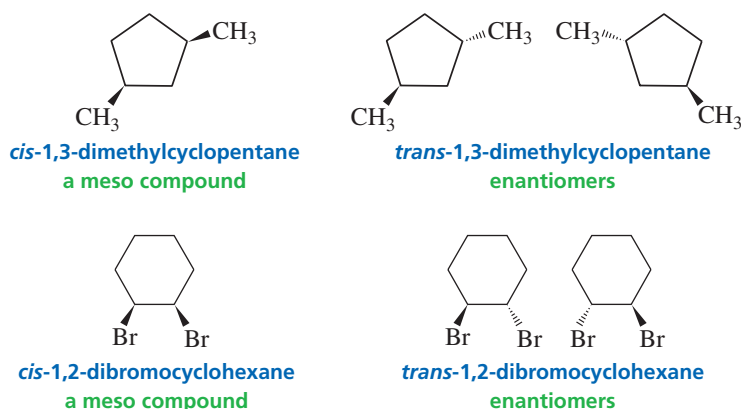
	Melting point, °C	Specific rotation	Solubility, g/100 g H_2O at 15 °C
(2*R*,3*R*)-(+)-Tartaric acid	171	+11.98	139
(2*S*,3*S*)-(−)-Tartaric acid	171	−11.98	139
(2*R*,3*S*)-Tartaric acid (meso)	146	0	125
(±)-Tartaric acid	206	0	139

In the case of cyclic compounds, the cis isomer will be a meso compound and the trans isomer will be a pair of enantiomers.

cis-1,3-dimethylcyclopentane
a meso compound

trans-1,3-dimethylcyclopentane
enantiomers

cis-1,2-dibromocyclohexane
a meso compound

trans-1,2-dibromocyclohexane
enantiomers

PROBLEM-SOLVING STRATEGY

Recognizing Whether a Compound Has a Stereoisomer That Is a Meso Compound

Which of the following compounds has a stereoisomer that is a meso compound?

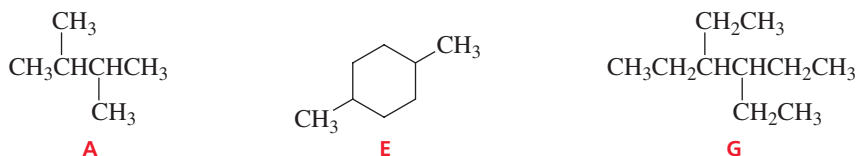
A 2,3-dimethylbutane
B 3,4-dimethylhexane
C 2-bromo-3-methylpentane
D 1,3-dimethylcyclohexane
E 1,4-dimethylcyclohexane
F 1,2-dimethylcyclohexane
G 3,4-diethylhexane
H 1-bromo-2-methylcyclohexane

Check each compound to see if it has the necessary requirements for having a stereoisomer that is a meso compound—that is, does it have two asymmetric centers, and if so, do they each have the same four substituents attached to them?

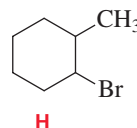
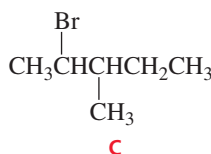
Compounds **A, E,** and **G** do *not* have a stereoisomer that is a meso compound because they do not have any asymmetric centers.

CH_3
$CH_3CHCHCH_3$
CH_3
A

CH_3
CH_3
E

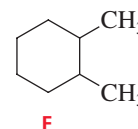
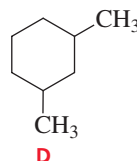
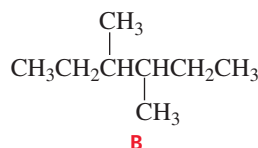
CH_2CH_3
$CH_3CH_2CHCHCH_2CH_3$
CH_2CH_3
G

Compounds **C** and **H** have two asymmetric centers. They do *not* have a stereoisomer that is a meso compound, however, because the two asymmetric centers in each compound are *not* bonded to the same four substituents.

Br
$CH_3CHCHCH_2CH_3$
CH_3
C

CH_3
Br
H

Compounds **B, D,** and **F** have two asymmetric centers, and the two asymmetric centers in each compound are bonded to the same four substituents. Therefore, these compounds have a stereoisomer that is a meso compound.

CH_3
$CH_3CH_2CHCHCH_2CH_3$
CH_3
B

CH_3
CH_3
D

CH_3
CH_3
F

Now use the strategy you have just learned to solve Problem 39.

PROBLEM 39♦

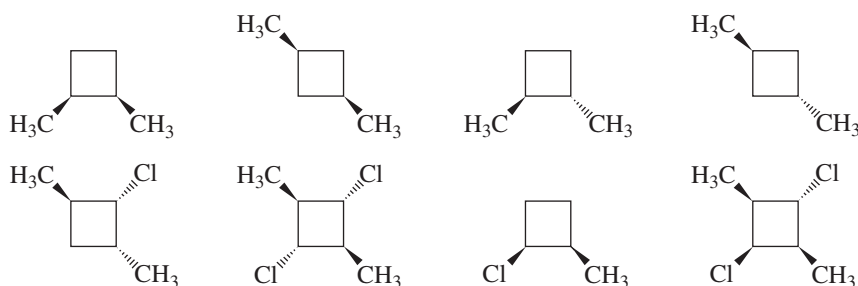
Which of the following compounds has a stereoisomer that is a meso compound?

A 2,4-dibromohexane
B 2,4-dibromopentane
C 2,4-dimethylpentane
D 1,3-dichlorocyclohexane
E 1,4-dichlorocyclohexane
F 1,2-dichlorocyclobutane

PROBLEM 40 Solved

Which of the following are optically active?

H_3C CH_3 | H_3C CH_3 | H_3C CH_3 | H_3C CH_3

H_3C Cl CH_3 | H_3C Cl Cl CH_3 | Cl CH_3 | H_3C Cl Cl CH_3

Solution In the *top row*, only the *third* compound is optically active. The first compound has a plane of symmetry, and an optically active compound cannot have a plane of symmetry; the second and fourth compounds do not have any asymmetric centers and each has a plane of symmetry. In the *bottom row*, the *first* and *third* compounds are optically active. The second and fourth compounds have a plane of symmetry.

PROBLEM 41

Draw all the stereoisomers for each of the following:

a. 1-chloro-3-methylpentane
b. 1-bromo-2-methylpropane
c. 3-chloro-3-methylpentane
d. 3,4-dichlorohexane
e. 1,2-dichlorocyclobutane
f. 1,3-dichlorocyclohexane
g. 1,4-dichlorocyclohexane
h. 1-bromo-2-chlorocyclobutane

4.13 RECEPTORS

A **receptor** is a protein that binds a particular molecule. Because proteins are chiral, a receptor will bind one enantiomer better than the other. In Figure 4.8, the receptor binds the *R* enantiomer, but it does not bind the *S* enantiomer.

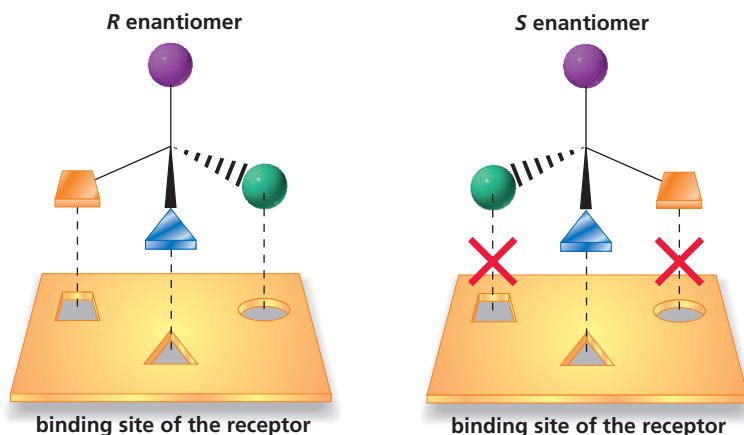



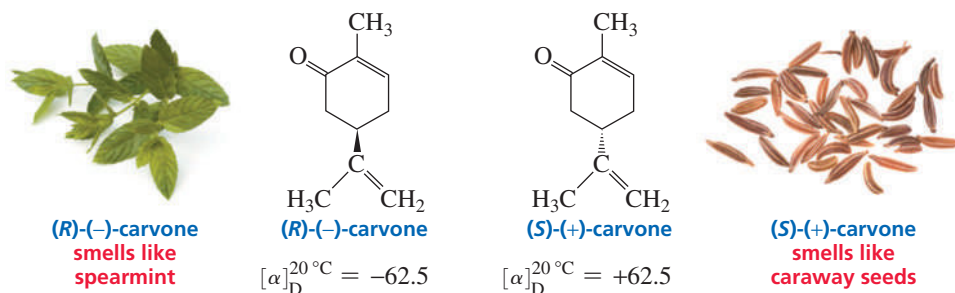
Figure 4.8
A schematic diagram showing why only one enantiomer is bound by a receptor. One enantiomer fits into the binding site and one does not.

The fact that a receptor typically recognizes only one enantiomer causes enantiomers to have different physiological properties. For example, receptors located on the exteriors of nerve cells in the nose are able to perceive and differentiate the estimated 10,000 smells to which they are exposed. The reason that (*R*)-(−)-carvone (found in spearmint oil) and (*S*)-(+)-carvone (the main constituent of caraway seed oil) have such different odors is that each enantiomer fits into a different receptor.

(*R*)-(−)-carvone
smells like
spearmint

(*R*)-(−)-carvone
$[\alpha]_D^{20\,°C} = -62.5$

(*S*)-(+)-carvone
$[\alpha]_D^{20\,°C} = +62.5$

(*S*)-(+)-carvone
smells like
caraway seeds

Many drugs exert their physiological activity by binding to cell-surface receptors. If the drug has an asymmetric center, the receptor can bind one of the enantiomers preferentially. Thus, enantiomers of a drug can have the same physiological activities, different degrees of the same activity, or very different activities, depending on the drug. For example, the enantiomers shown here have very different physiological activities.

the active ingredient
in Vicks Vapor Inhaler®

methamphetamine
"speed"

Dr. Frances O. Kelsey receives the President's medal for Distinguished Federal Civilian Service from President John F. Kennedy in 1962 for preventing the sale of thalidomide. Kelsey was born in British Columbia in 1914. She received a B.Sc. in 1934 and a M.Sc. in pharmacology in 1936 from McGill University. In 1938, she received a Ph.D. and an M.D. from the University of Chicago, where she became a member of the faculty. She married a fellow faculty member and they had two daughters. She joined the FDA in 1960 and worked there until 2005, when she retired at the age of 90. Each year the FDA selects a staff member to receive the Dr. Frances O. Kelsey Award for Excellence and Courage in Protecting Public Health.

PROBLEM 42♦

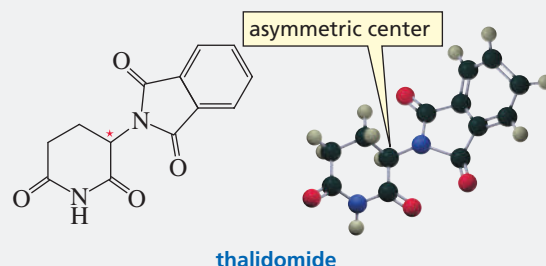
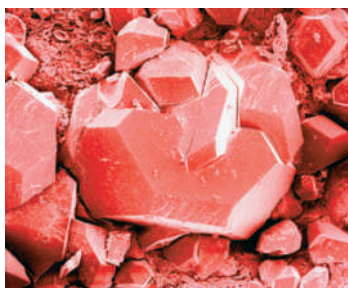
Limonene exists as two different stereoisomers. The *R* enantiomer is found in oranges and lemons, and the *S* enantiomer is found in spruce trees. Which of the following is found in oranges and lemons?

(+)-limonene (−)-limonene

The Enantiomers of Thalidomide

Thalidomide was developed in West Germany and was first marketed (as Contergan) in 1957 for insomnia, tension, and morning sickness during pregnancy. At that time it was available in more than 40 countries but had not been approved for use in the United States because Frances O. Kelsey, a physician for the Food and Drug Administration (FDA), had insisted upon additional tests to explain a British study that had found nervous system side effects.

The (+)-isomer of thalidomide has stronger sedative properties, but the commercial drug was a racemic mixture. No one knew that the (−)-isomer is a teratogen—a compound that causes congenital deformations—until women who had been given the drug during the first three months of pregnancy gave birth to babies with a wide variety of defects, with deformed limbs being the most common. By the time the danger was recognized and the drug withdrawn from the market on November 27, 1961, about 10,000 children had been damaged. It was eventually determined that the (+)-isomer also has mild teratogenic activity and that each of the enantiomers can racemize (interconvert) in the body. Thus, it is not clear whether the birth defects would have been less severe if the women had been given only the (+)-isomer. Because thalidomide damaged fast growing cells in the developing fetus, it has recently been approved—with restrictions and with tight controls—for the eradication of certain kinds of cancer cells.

thalidomide

Louis Pasteur (1822–1895) was the first to demonstrate that microbes cause specific diseases. He showed that the microorganisms that cause grape juice to ferment, producing wine, also cause wine to become sour. Gently heating the wine after fermentation, a process called pasteurization, kills the organisms so they cannot sour the wine.

4.14 HOW ENANTIOMERS CAN BE SEPARATED

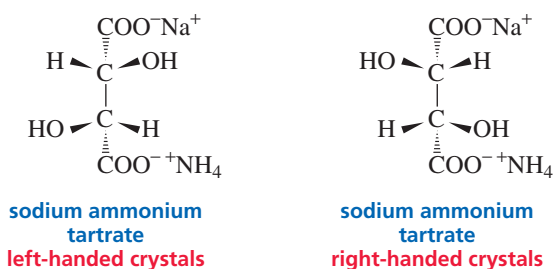
Enantiomers cannot be separated by the usual separation techniques such as fractional distillation or crystallization because their identical boiling points and solubilities cause them to distill or crystallize simultaneously.

Louis Pasteur was the first to succeed in separating a pair of enantiomers. While working with crystals of sodium ammonium tartrate, he noted that the crystals were not identical—some were "right-handed" and some were "left-handed." After painstakingly separating the two kinds of crystals with a pair of tweezers, he found that a solution of the right-handed crystals rotated the plane of polarization of plane-polarized light clockwise, whereas a solution of the left-handed crystals rotated it counterclockwise.

COO^-Na^+
H — C — OH
HO — C — H
$COO^- \, ^+NH_4$

sodium ammonium tartrate
left-handed crystals

COO^-Na^+
HO — C — H
H — C — OH
$COO^- \, ^+NH_4$

sodium ammonium tartrate
right-handed crystals

Pasteur's experiment gave rise to a new chemical term. Tartaric acid is obtained from grapes, so it was also called racemic acid (*racemus* is Latin for "a bunch of grapes"). This is how a mixture of equal amounts of enantiomers came to be known as a **racemic mixture** (Section 4.9). Separation of enantiomers is called the **resolution of a racemic mixture.**

Separating enantiomers by hand, as Pasteur did, is not a universally useful method because few compounds form asymmetric crystals. Until relatively recently, separating enantiomers was a very tedious process. Fortunately, enantiomers can now be separated relatively easily by a technique called **chromatography.**

In this method, the mixture to be separated is dissolved in a solvent and the solution is passed through a column packed with a chiral material that adsorbs organic compounds. The two enantiomers (red and purple discs) will move through the column at different rates because they will have different affinities for the chiral material—just

Crystals of potassium hydrogen tartrate (also called cream of tartar), a naturally occurring salt found in wines. It is used in place of lemon or vinegar in some recipies. Most fruits produce citric acid, but grapes produce large quantities of tartaric acid instead.

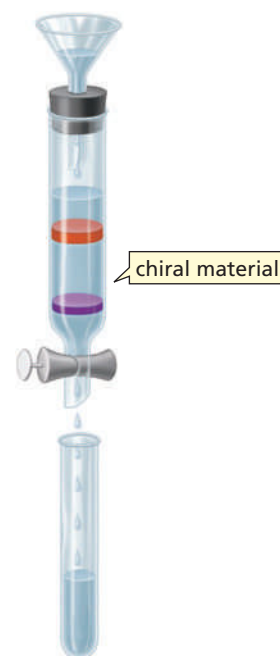
as a right hand prefers a right-hand glove to a left-hand glove—so one enantiomer will emerge from the column before the other. Because it is now so much easier to separate enantiomers, many drugs are being sold as single enantiomers rather than as racemic mixtures (see the box "Chiral Drugs").

The chiral material used in chromatography is one example of a **chiral probe,** something capable of distinguishing between enantiomers. A polarimeter is another example of a chiral probe (Section 4.9).

Chiral Drugs

Until relatively recently, most drugs with one or more asymmetric centers have been marketed as racemic mixtures because of the difficulty of synthesizing single enantiomers and the high cost of separating enantiomers. In 1992, however, the Food and Drug Administration (FDA) issued a policy statement encouraging drug companies to use recent advances in synthesis and separation techniques to develop single-enantiomer drugs. Now most new drugs sold are single enantiomers. Drug companies have been able to extend their patents by marketing a single enantiomer of a drug that was previously available only as a racemate.

If a drug is sold as a racemate, the FDA requires both enantiomers to be tested because drugs bind to receptors and, since receptors are chiral, the enantiomers of a drug can bind to different receptors (Section 4.13). Therefore, enantiomers can have similar or very different physiological properties. Examples are numerous. Testing has shown that (*S*)-(+)-ketamine is four times more potent an anesthetic than (*R*)-(−)-ketamine, and the disturbing side effects are apparently associated only with the (*R*)-(−)-enantiomer. Only the *S* isomer of the beta-blocker propranolol shows activity; the *R* isomer is inactive. The *S* isomer of Prozac, an antidepressant, is better at blocking serotonin but is used up faster than the *R* isomer. The activity of ibuprofen, the popular analgesic marketed as Advil, Nuprin, and Motrin, resides primarily in the (*S*)-(+)-enantiomer. Heroin addicts can be maintained with (−)-α-acetylmethadol for a 72-hour period compared to 24 hours with racemic methadone. This means less frequent visits to an outpatient clinic, because a single dose can keep an addict stable through an entire weekend.

Prescribing a single enantiomer spares the patient from having to metabolize the less potent enantiomer and decreases the chance of unwanted drug interactions. Drugs that could not be given as racemates because of the toxicity of one of the enantiomers can now be used. For example, (*S*)-penicillamine can be used to treat Wilson's disease even though (*R*)-penicillamine causes blindness.

SOME IMPORTANT THINGS TO REMEMBER

- **Stereochemistry** is the field of chemistry that deals with the structures of molecules in three dimensions.
- **Isomers** are compounds with the same molecular formula but different structures.
- **Constitutional isomers** differ in the way their atoms are connected.
- **Stereoisomers** differ in the way their atoms are arranged in space.
- There are two kinds of stereoisomers: **cis–trans isomers** and isomers that contain **asymmetric centers.**
- Because rotation about the bonds in a cyclic compound is restricted, disubstituted cyclic compounds exist as **cis–trans isomers.** The **cis isomer** has the substituents on the same side of the ring; **the trans isomer** has the substituents on opposite sides of the ring.
- Because rotation about a double bond is restricted, an alkene can exist as **cis–trans isomers.** The **cis isomer** has its hydrogens on the same side of the double bond; the **trans isomer** has its hydrogens on opposite sides of the double bond.
- The ***Z*** **isomer** has the high-priority groups on the same side of the double bond; the ***E*** **isomer** has the high-priority groups on opposite sides of the double bond. The relative priorities depend on the atomic numbers of the atoms bonded directly to the sp^2 carbon.
- A **chiral** molecule has a nonsuperimposable mirror image; an **achiral** molecule has a superimposable mirror image.
- An **asymmetric center** is an atom bonded to four different atoms or groups.

- **Enantiomers** are nonsuperimposable mirror images.
- **Diastereomers** are stereoisomers that are not enantiomers.
- Enantiomers have identical physical and chemical properties; diastereomers have different physical and chemical properties.
- The letters ***R*** and ***S*** indicate the **configuration** about an asymmetric center.
- Chiral compounds are **optically active;** achiral compounds are **optically inactive.**
- If one enantiomer rotates the plane of polarization clockwise (+), its mirror image will rotate it the same amount counterclockwise (−).
- Each optically active compound has a characteristic **specific rotation.**
- A **racemic mixture,** indicated by (±), is a mixture of equal amounts of two enantiomers; it is optically inactive.
- In the case of compounds with two asymmetric centers, enantiomers have the opposite configuration at both asymmetric centers; diastereomers have the same configuration at one asymmetric center and the opposite configuration at the other asymmetric center.
- A **meso compound** has two or more asymmetric centers and a plane of symmetry; it is optically inactive.
- A compound with the same four groups bonded to two different asymmetric centers will have three stereoisomers—namely, a meso compound and a pair of enantiomers.

PROBLEMS

43. Which of the following have an asymmetric center?

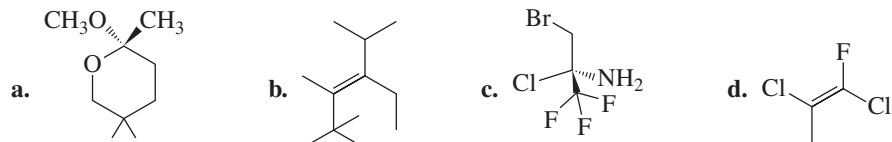
CHF_2COOH $CBr_2ClCOOH$ $CHClBrF$ $CHFClCH_3$ CBr_3NH_2

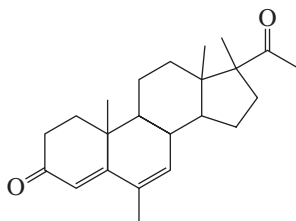
44. Draw all possible stereoisomers for each of the following compounds. Indicate if no stereoisomers are possible.

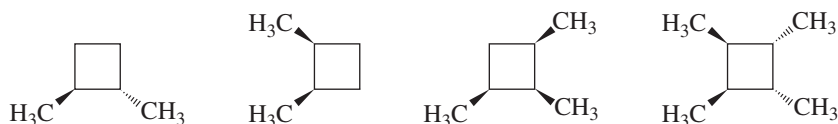
a. 2-bromo-4-methylpentane
b. 2-bromo-4-chloropentane
c. 3-heptene
d. 1-bromo-4-methylcyclohexane
e. 1-bromo-3-chlorocyclobutane
f. 2-iodopentane
g. 3,3-dimethylpentane
h. 3-chloro-1-butene

45. Disregarding cis-trans isomers, draw the structures of all alkenes with molecular formula C_5H_{10}. Which ones can exist as cis-trans isomers?

46. Name the following compounds using *R,S* and *E,Z* (Sections 4.2 and 4.7) designations where necessary:

a. **b.** **c.** **d.**

47. Of all the possible cyclooctanes that have one chloro substituent and one methyl substituent, which ones do *not* have any asymmetric centers?

48. Medrogestone is a drug used in the treatment of cancer. How many asymmetric centers does **Medrogestone** have?

Medrogestone

49. Which of the following is optically active?

50. Are the following pairs of structures identical compounds, enantiomers, diastereomers, or constitutional isomers?

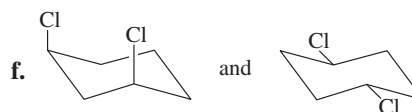
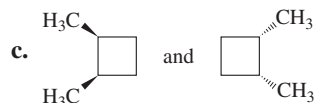
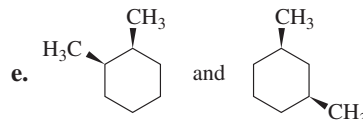
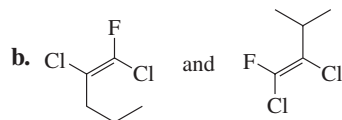
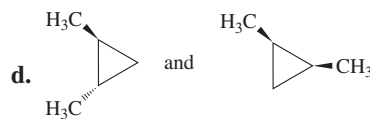
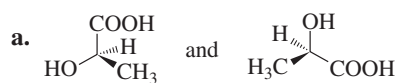
a. COOH, H, HO, CH_3 and H, OH, H_3C, COOH

b. F, Cl, Cl and F, Cl, Cl

c. H_3C, H_3C and CH_3, CH_3

d. H_3C, H_3C and H_3C, CH_3

e. CH_3, H_3C and CH_3, CH_3

f. Cl, Cl and Cl, Cl

51. Assign relative priorities to each set of substituents:

a. $-CH_2CH_2CH_3$ $\quad -CH(CH_3)_2$ $\quad -CH{=}CH_2$ $\quad -CH_3$

b. $-CH_2NH_2$ $\quad -NH_2$ $\quad -OH$ $\quad -CH_2OH$

c. $-C({=}O)CH_3$ $\quad -CH{=}CH_2$ $\quad -Cl$ $\quad -C{\equiv}N$

52. Which of the following compounds have an achiral stereoisomer?

a. 2,3-dichlorobutane **b.** 2,3-dichloropentane **c.** 2,4-dibromopentane **d.** 2,3-dibromopentane

53. Draw the stereoisomers of 2,4-dichlorohexane. Indicate pairs of enantiomers and pairs of diastereomers.

54. Do the following compounds have the *E* or the *Z* configuration?

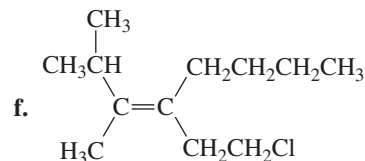
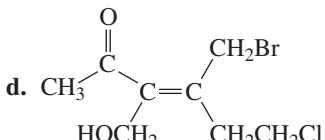
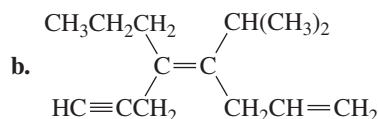
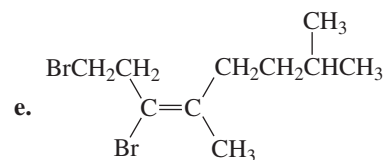
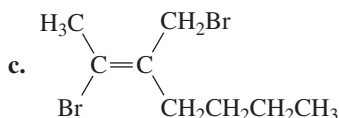
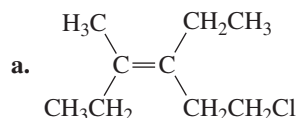
a. H_3C, CH_2CH_3 / C=C / CH_3CH_2, CH_2CH_2Cl

b. $CH_3CH_2CH_2$, $CH(CH_3)_2$ / C=C / $HC{\equiv}CCH_2$, $CH_2CH{=}CH_2$

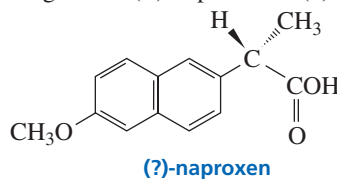
c. H_3C, CH_2Br / C=C / Br, $CH_2CH_2CH_2CH_3$

d. $CH_3C({=}O)$, CH_2Br / C=C / $HOCH_2$, CH_2CH_2Cl

e.

f. $CH_3CH(CH_3)$, $CH_2CH_2CH_2CH_3$ / C=C / H_3C, CH_2CH_2Cl

55. The stereoisomer of naproxen that is the active ingredient in Aleve and in several other over-the-counter nonsteroidal anti-inflammatory drugs is shown below. Is the active ingredient (*R*)-naproxen or (*S*)-naproxen?

H, CH_3, C, COH, O, CH_3O

(?)-naproxen

56. A solution of an unknown compound (3.0 g of the compound in 20 mL of solution), when placed in a polarimeter tube 2.0 dm long, was found to rotate the plane of polarized light 180° in a counterclockwise direction. What is the specific rotation of the compound?

57. Explain how *R* and *S* are related to (+) and (−).

58. Are the following pairs identical, enantiomers, diastereomers, or constitutional isomers?

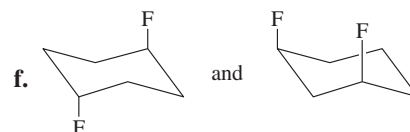
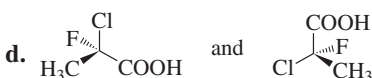
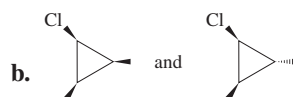
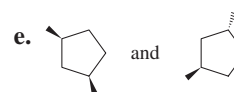
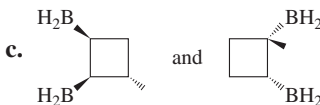
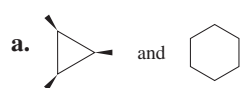
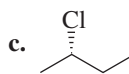
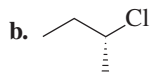
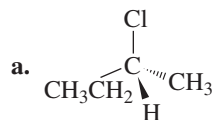
a.

b. Cl and Cl

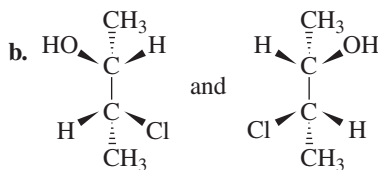
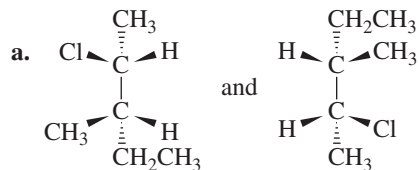
c. H_2B, H_2B and BH_2, BH_2

d. Cl, F, H_3C, COOH and COOH, F, Cl, CH_3

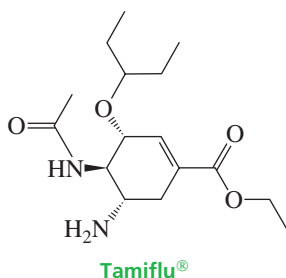
e.

f. F, F and F, F

59. Indicate whether each of the following structures is (*R*)-2-chlorobutane or (*S*)-2-chlorobutane.

a. Cl; C; CH_3CH_2; CH_3; H **b.** Cl **c.** Cl

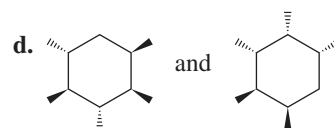
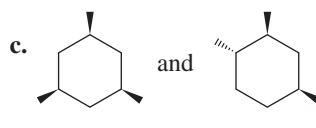
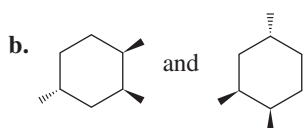
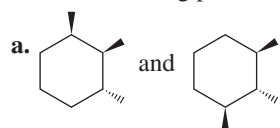
60. Indicate whether the following pairs of structures represent identical compounds or enantiomers:

a. CH_3; Cl; C; H; C; CH_3; H; CH_2CH_3 and CH_2CH_3; H; C; CH_3; C; H; Cl; CH_3 **b.** CH_3; HO; C; H; C; H; Cl; CH_3 and CH_3; H; C; OH; C; Cl; H; CH_3

61. Tamiflu is used for the prevention and treatment of flu. What is the configuration of each of its asymmetric centers? (How Tamiflu Works is explained in Chapter 18.)

O; O; O; HN; O; H_2N

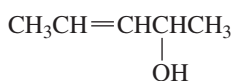
Tamiflu®

62. Are the following pairs identical, enantiomers, diastereomers, or constitutional isomers?

a. and

b. and **c.** and **d.** and

63. Draw structures for each of the following:

a. (*S*)-1-bromo-1-chlorobutane
b. an achiral isomer of 1,2-dimethylcyclohexane
c. a chiral isomer of 1,2-dibromocyclobutane

64. The following compound has only one asymmetric center. Why, then, does it have four stereoisomers?

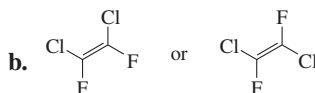
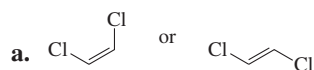
$$CH_3CH{=}CH\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$$

65. a. Draw all the isomers with molecular formula C_6H_{12} that contain a cyclobutane ring. (*Hint:* There are seven.)

b. Name the compounds without specifying the configuration of any asymmetric centers.

c. Identify:

1. constitutional isomers
2. stereoisomers
3. cis–trans isomers
4. chiral compounds
5. achiral compounds
6. meso compounds
7. enantiomers
8. diastereomers

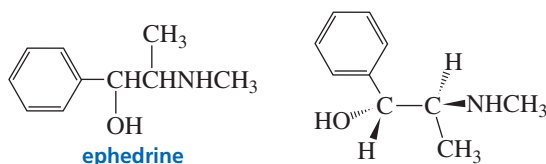
66. Which compound has the greater dipole moment?

a. Cl, Cl or Cl, Cl **b.** Cl, Cl, F, F or F, Cl, Cl, F

67. For many centuries, the Chinese have used extracts from a group of herbs known as ephedra to treat asthma. A compound named ephedrine has been isolated from these herbs and found to be a potent dilator of air passages in the lungs.

a. How many stereoisomers does ephedrine have?

b. The stereoisomer shown here is the one that is pharmacologically active. What is the configuration of each of the asymmetric centers?

$C_6H_5CH(OH)CH(CH_3)NHCH_3$

ephedrine

68. Citrate synthase, one of the enzymes in the series of enzyme-catalyzed reactions known as the citric acid cycle (Section 19.8), catalyzes the synthesis of citric acid from oxaloacetic acid and acetyl-CoA. If the synthesis is carried out with acetyl-CoA that contains radioactive carbon (^{14}C) in the indicated position (Section 1.1), the isomer shown here is obtained. (If two isotopes—atoms with the same atomic number, but different mass numbers—are being compared, the one with the greater mass number has the higher priority.)

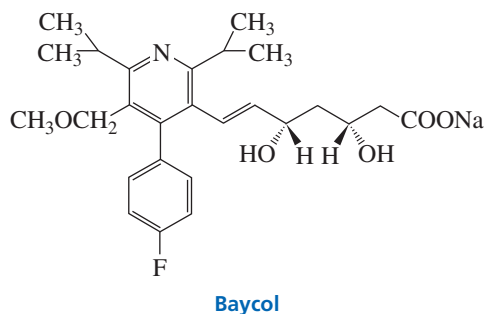
$HOOCCH_2C(=O)COOH$ + $^{14}CH_3C(=O)SCoA$ —citrate synthase→ citric acid ($^{14}CH_2COOH$, HO, COOH, CH_2COOH on C)

oxaloacetic acid; acetyl-CoA; citric acid

a. Which stereoisomer of citric acid is synthesized, *R* or *S*?

b. If the acetyl-CoA used in the synthesis contains ^{12}C instead of ^{14}C, will the product of the reaction be chiral or achiral?

69. Baycol, Lipobay is a cholesterol-reducing drug that has now been banned from many markets for its adverse side effects. What is the configuration of each of the asymmetric centers?

Baycol

5 Alkenes

Nomenclature, Stability, and an Introduction to Reactivity • Thermodynamics and Kinetics

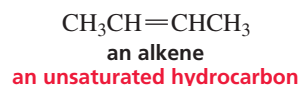
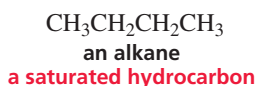
the gothic tower of Glasgow University overlooking the River Kelvin (see page 187)

Some of the things you will learn about in this chapter are how the Kelvin temperature scale got its name, how trans fats get into our food, how insect populations can be controlled, and how compounds in biological systems recognize each other.

In Chapter 3, we saw that alkanes are hydrocarbons that contain only carbon–carbon *single* bonds. Now we will take a look at **alkenes,** hydrocarbons that contain a carbon–carbon *double* bond.

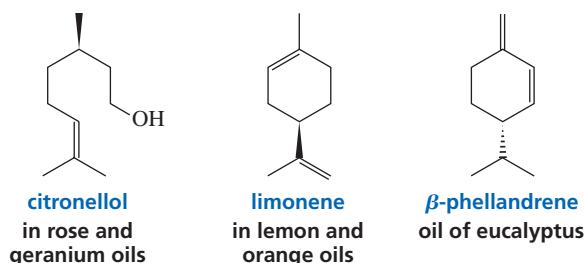
Because *alkanes* contain the maximum number of C—H bonds possible—that is, they are saturated with hydrogen—they are called **saturated hydrocarbons.** In contrast, *alkenes* are called **unsaturated hydrocarbons** because they have fewer than the maximum number of hydrogens.

$CH_3CH_2CH_2CH_3$	$CH_3CH{=}CHCH_3$
an alkane	**an alkene**
a saturated hydrocarbon	an unsaturated hydrocarbon

Tomatoes are shipped green so they will arrive unspoiled. Ripening starts when they are exposed to ethene.

Alkenes play many important roles in biology. For example, ethene ($H_2C{=}CH_2$), the smallest alkene, is a plant hormone—a compound that controls growth and other changes in the plant's tissues. Among other things, ethene affects seed germination, flower maturation, and fruit ripening. Many of the flavors and fragrances produced by plants also belong to the alkene family.

citronellol
in rose and geranium oils

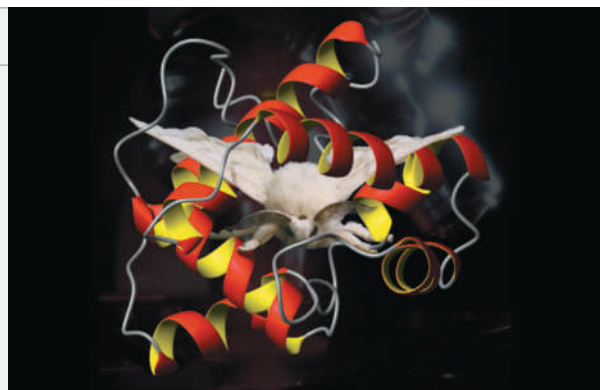
limonene
in lemon and orange oils

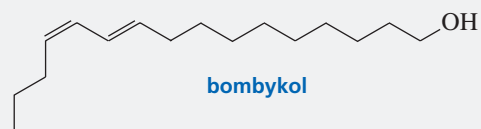
β-phellandrene
oil of eucalyptus

We have already looked at the structures of alkenes (Section 4.1). Now we will see how alkenes are named and then we will examine a reaction of an alkene, paying close attention to the steps by which the reaction occurs and the energy changes that accompany them. We will then use our knowledge of the energy changes that occur in a reaction to understand the factors that affect the stability of an alkene. You will see that some of the discussion in this chapter revolves around concepts with which you are already familiar, while some of the information is new and will broaden the foundation of knowledge that you will be building on in subsequent chapters.

Pheromones

Insects communicate by releasing pheromones—chemical substances that other insects of the same species detect with their antennae. Many of the sex, alarm, and trail pheromones are alkenes or are synthesized from alkenes.

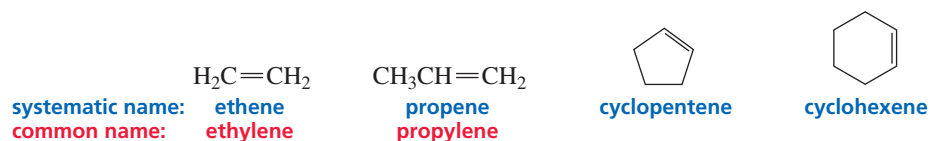
Bombykol is the sex pheromone of the silk moth (*bombyx mori*). Molecules of bombykol diffuse through open pores in the male moth's antennae. When bombykol binds to its receptor, an electrical charge is produced that causes a nerve impulse to be sent to the brain. Bombykol, however, is a nonpolar molecule and has to cross an aqueous solution to get to its receptor. This problem is solved by the pheromone-binding protein. The protein binds bombykol in a hydrophobic pocket and then carries it to the receptor. The area around the receptor is relatively acidic, and the decrease in pH causes the pheromone-binding protein to unfold and release bombykol to the receptor.

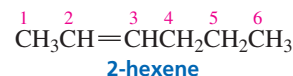
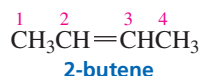
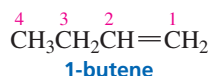
Interfering with an insect's ability to send or receive chemical signals is an environmentally safe way to control insect populations. For example, traps containing synthetic sex attractants have been used to capture such crop-destroying insects such as the gypsy moth and the boll weevil.

Bombyx mori superimposed on the pheromone-binding protein.

bombykol

5.1 THE NOMENCLATURE OF ALKENES

The **functional group** is the center of reactivity in an organic molecule. In an alkene, the double bond is the functional group. The IUPAC system uses a suffix to denote certain functional groups. The systematic name of an alkene, for example, is obtained by replacing the *ane* at the end of the parent hydrocarbon's name with the suffix *ene*. Thus, a two-carbon alkene is called ethene, and a three-carbon alkene is called propene. Ethene also is frequently called by its common name: ethylene.

$CH_3CH{=}CH_2$

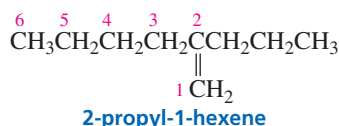
systematic name:	ethene	propene	cyclopentene	cyclohexene
common name:	ethylene	propylene		

The following rules are used to name a compound with a functional group suffix:

1. The longest continuous chain containing the functional group (in this case, the carbon–carbon double bond) is numbered in the direction that gives the functional group suffix the lowest possible number. For example, 1-butene signifies that the double bond is between the first and second carbons of butene; 2-hexene signifies that the double bond is between the second and third carbons of hexene. (The four alkene names shown on page 177 do not need a number because there is no ambiguity.)

Number the longest continuous chain containing the functional group in the direction that gives the functional group suffix the lowest possible number.

$\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H{=}\overset{1}{C}H_2$ **1-butene**

$\overset{1}{C}H_3\overset{2}{C}H{=}\overset{3}{C}H\overset{4}{C}H_3$ **2-butene**

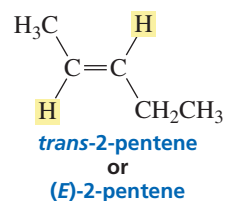
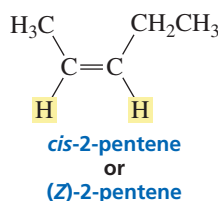
$\overset{1}{C}H_3\overset{2}{C}H{=}\overset{3}{C}H\overset{4}{C}H_2\overset{5}{C}H_2\overset{6}{C}H_3$ **2-hexene**

$\overset{6}{C}H_3\overset{5}{C}H_2\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}(={}^{1}CH_2)CH_2CH_2CH_3$ **2-propyl-1-hexene**

the longest continuous chain has eight carbons but the longest continuous chain containing the functional group has six carbons, so the parent name of the compound is hexene

Notice that 1-butene does not have a common name. You might be tempted to call it "butylene," which is analogous to "propylene" for propene. Butylene, however, is not an appropriate name because it could signify either 1-butene or 2-butene, and a name must be unambiguous.

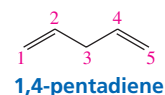
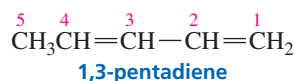
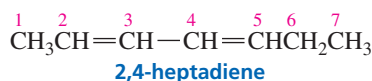
The stereoisomers of an alkene are named using a *cis* or *trans* (or *E* or *Z*) prefix (in italics).

H_3C, CH_2CH_3 / C=C / H, H
***cis*-2-pentene** **or** **(*Z*)-2-pentene**

H_3C, H / C=C / H, CH_2CH_3
***trans*-2-pentene** **or** **(*E*)-2-pentene**

2. For a compound with two double bonds, the "ne" ending of the corresponding alkane is replaced with "diene."

$\overset{1}{C}H_3\overset{2}{C}H{=}\overset{3}{C}H{-}\overset{4}{C}H{=}\overset{5}{C}H\overset{6}{C}H_2\overset{7}{C}H_3$ **2,4-heptadiene**

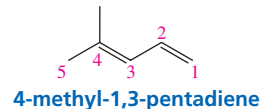
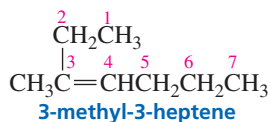
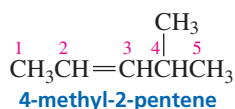
$\overset{5}{C}H_3\overset{4}{C}H{=}\overset{3}{C}H{-}\overset{2}{C}H{=}\overset{1}{C}H_2$ **1,3-pentadiene**

1,4-pentadiene

3. The name of a substituent is stated before the name of the longest continuous chain that contains the functional group, together with a number to designate the carbon to which the substituent is attached. Notice that *when a compound's name contains both a functional group suffix and a substituent, the functional group suffix gets the lowest possible number.*

When there are both a functional group suffix and a substituent, the functional group suffix gets the lowest possible number.

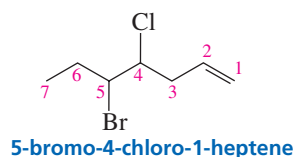
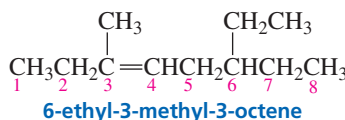
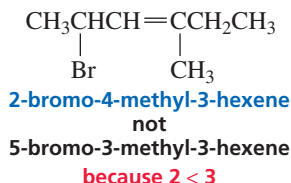
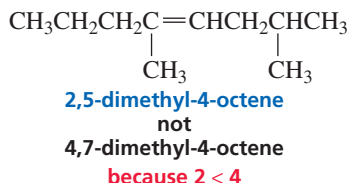
$\overset{1}{C}H_3\overset{2}{C}H{=}\overset{3}{C}H\overset{4}{C}H(CH_3)\overset{5}{C}H_3$ **4-methyl-2-pentene**

$CH_3\overset{3}{C}(\overset{2}{C}H_2\overset{1}{C}H_3){=}\overset{4}{C}H\overset{5}{C}H_2\overset{6}{C}H_2\overset{7}{C}H_3$ **3-methyl-3-heptene**

4-methyl-1,3-pentadiene

4. If a chain has more than one substituent, the substituents are stated in alphabetical order, using the same rules for alphabetizing discussed in Section 3.2. Then the appropriate number is assigned to each substituent.

Substituents are stated in alphabetical order.

$\overset{1}{C}H_3\overset{2}{C}H_2\overset{3}{C}(CH_3){=}\overset{4}{C}H\overset{5}{C}H_2\overset{6}{C}H(CH_2CH_3)\overset{7}{C}H_2\overset{8}{C}H_3$ **6-ethyl-3-methyl-3-octene**

Cl, Br **5-bromo-4-chloro-1-heptene**

5. If counting in either direction results in the same number for the alkene functional group suffix, the correct name is the one containing the lowest substituent number. For example, the compound shown next on the left is a 4-octene whether the longest continuous chain is numbered from left to right or from right to left. If you number from left to right, then the substituents are at positions 4 and 7, but if you number from right to left, they are at positions 2 and 5. Of those four substituent numbers, 2 is the lowest, so the compound is named 2,5-dimethyl-4-octene.

$CH_3CH_2CH_2C(CH_3){=}CHCH_2CH(CH_3)CH_3$

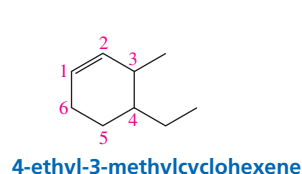
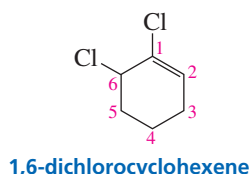
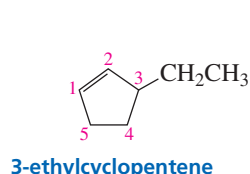
2,5-dimethyl-4-octene
not
4,7-dimethyl-4-octene
because 2 < 4

$CH_3CH(Br)CH{=}C(CH_3)CH_2CH_3$

2-bromo-4-methyl-3-hexene
not
5-bromo-3-methyl-3-hexene
because 2 < 3

A substituent receives the lowest possible number only if there is no functional group suffix or if the same number for the functional group suffix is obtained in both directions.

6. A number is not needed to denote the position of the double bond in a cyclic alkene because the ring is always numbered so that the double bond is between carbons 1 and 2. To assign numbers to any substituents, count around the ring in the direction (clockwise or counterclockwise) that puts the lowest number into the name.

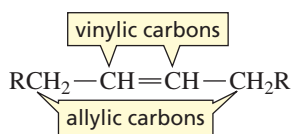
3-ethylcyclopentene **1,6-dichlorocyclohexene** **4-ethyl-3-methylcyclohexene**

Notice that 1,6-dichlorocyclohexene is *not* called 2,3-dichlorocyclohexene because the former has the lowest substituent number (1), even though it does not have the lowest sum of substituent numbers ($1 + 6 = 7$ versus $2 + 3 = 5$).

Remember that the name of a substituent is stated *before* the name of the parent hydrocarbon, and the functional group suffix is stated *after* the name of the parent hydrocarbon.

methyl, chloro, etc. → **[substituent] [parent hydrocarbon] [functional group suffix]** ← ene

The sp^2 carbons of an alkene are called **vinylic carbons.** An sp^3 carbon that is adjacent to a vinylic carbon is called an **allylic carbon.**

vinylic carbons

$RCH_2{-}CH{=}CH{-}CH_2R$

allylic carbons

A hydrogen bonded to a vinylic carbon is called a **vinylic hydrogen,** and a hydrogen bonded to an allylic carbon is called an **allylic hydrogen.**

PROBLEM 1♦

a. How many vinylic hydrogens does the preceding compound have?
b. How many allylic hydrogens does it have?

Two groups containing a carbon–carbon double bond are used in common names—the **vinyl group** and the **allyl group.** The vinyl group is the smallest possible group that contains a vinylic carbon and the allyl group is the smallest possible group that contains an allylic carbon. When “vinyl” or “allyl” is used in a name, the substituent must be attached to the vinylic or allylic carbon, respectively.

$CH_2{=}CH{-}$ the vinyl group

$CH_2{=}CHCH_2{-}$ the allyl group

	$CH_2{=}CHCl$	$CH_2{=}CHCH_2Br$
common name:	vinyl chloride	allyl bromide
systematic name:	chloroethene	3-bromopropene

PROBLEM 2♦

Draw the structure for each of the following:

a. 3,3-dimethylcyclopentene

b. 6-bromo-2,3-dimethyl-2-hexene

c. ethyl vinyl ether

d. allyl alcohol

PROBLEM 3♦

What is each compound's systematic name?

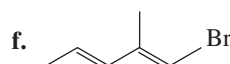
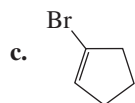
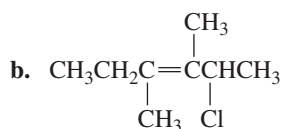
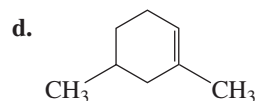
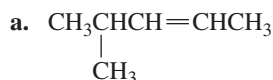
a. $CH_3CHCH{=}CHCH_3$ (with CH_3 on C-2)

b. $CH_3CH_2C{=}CCHCH_3$ (with CH_3 on C-3, CH_3 on C-4, Cl on C-5)

c. Br (cyclopentene with Br on the double-bond carbon)

d. CH_3 CH_3 (cyclohexene with two methyl groups)

e. $BrCH_2CH_2CH{=}CCH_3$ (with CH_2CH_3 on the C=C carbon)

f. Br (skeletal structure)

5.2 HOW AN ORGANIC COMPOUND REACTS DEPENDS ON ITS FUNCTIONAL GROUP

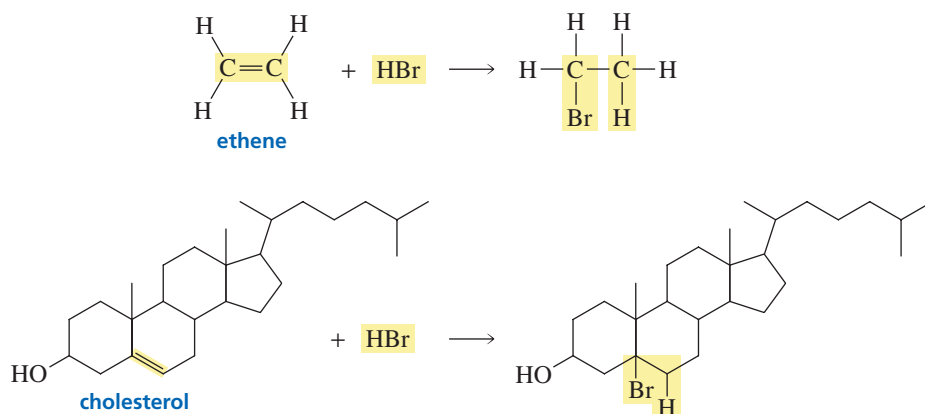
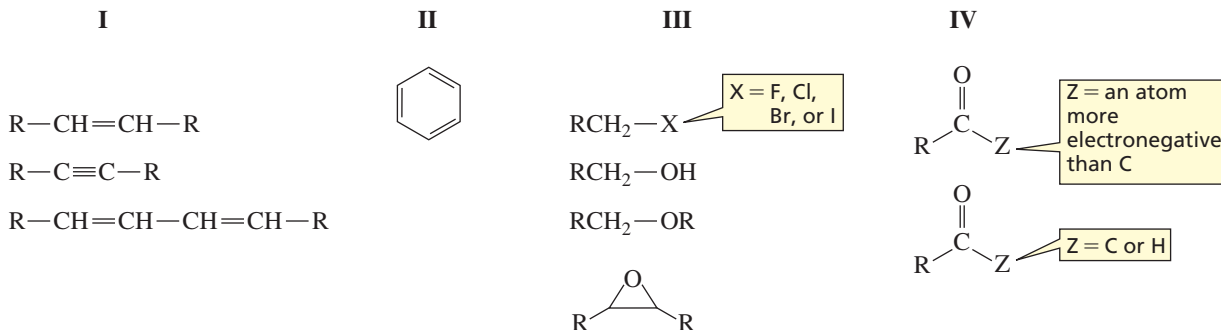
There are many millions of organic compounds (and more being made each year). If you had to memorize how each of them reacts, studying organic chemistry would not be a very pleasant experience. Fortunately, organic compounds can be divided into families, and all the members of a family react in the same way.

The family that an organic compound belongs to is determined by its functional group. The **functional group** determines the kinds of reactions a compound will undergo. You are already familiar with the functional group of an alkene: the carbon–carbon double bond. All compounds with a carbon–carbon double bond react in the same way, whether the compound is a small molecule like ethene or a large molecule like cholesterol. (You will find a table of common functional groups inside the front cover of this book.)

$H_2C{=}CH_2$ + HBr ⟶ $H{-}CH_2{-}CH_2Br$ … (H–C(H)(Br)–C(H)(H)–H)

ethene

cholesterol + HBr ⟶ (product with Br and H added across the double bond)

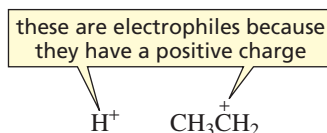
cholesterol

What makes learning organic chemistry even easier is that all the families of organic compounds can be placed in one of four groups, and all the families in a group react in similar ways. We will start our study of reactions by looking at the reactions of alkenes, a family that belongs to the first of the four groups.

5.3 HOW ALKENES REACT • CURVED ARROWS SHOW THE FLOW OF ELECTRONS

When you study the reactions of a particular functional group, you need to understand *why* the functional group reacts the way it does. It is not enough to look at the two reactions shown in Section 5.2 and see that the carbon–carbon double bond reacts with HBr to form a product in which the H and Br atoms have taken the place of the π bond. You need to understand why the reaction occurs. If you understand the reason for each functional group's reactivity, you will reach the point where you can look at an organic compound and be able to predict the kind of reactions it will undergo.

In essence, organic chemistry is all about the interaction between *electron-rich* atoms or molecules and *electron-deficient* atoms or molecules. These are the forces that make chemical reactions happen. So each time you encounter a new functional group, remember that the reactions it undergoes can be explained by a very simple rule:

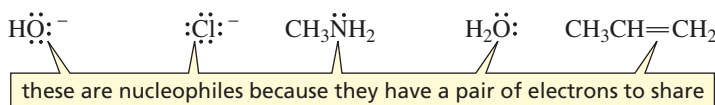
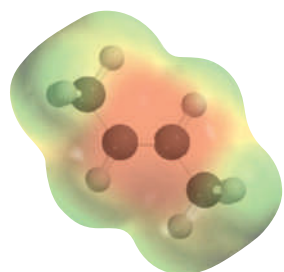
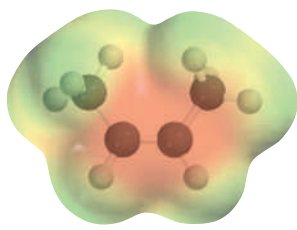
> *Electron-deficient atoms or molecules are attracted to electron-rich atoms or molecules.*

Therefore, to understand how a functional group reacts, you must first learn to recognize electron-deficient and electron-rich atoms and molecules.

An electron-deficient atom or molecule is called an **electrophile.** Literally, "electrophile" means "electron loving" (*phile* is the Greek suffix for "loving"). An electrophile looks for a pair of electrons. It is easy to recognize an electrophile because it generally has a positive charge.

Electron-deficient atoms or molecules are attracted to electron-rich atoms or molecules.

An electron-rich atom or molecule is called a **nucleophile.** A nucleophile has a pair of electrons it can share. Nucleophiles and electrophiles attract each other (like negative and positive charges) because nucleophiles have electrons to share and electrophiles are seeking electrons. Thus, the preceding rule can be restated as *nucleophiles react with electrophiles.*

$HO{:}^-$ $\quad {:}Cl{:}^-$ $\quad CH_3NH_2$ $\quad H_2O{:}$ $\quad CH_3CH{=}CH_2$

these are nucleophiles because they have a pair of electrons to share

A nucleophile reacts with an electrophile.

trans-2-butene

cis-2-butene

Let's now see how the rule "*nucleophiles react with electrophiles*" allows us to predict the characteristic reaction of an alkene. We have seen that the π bond of an alkene consists of a cloud of electrons above and below the σ bond. As a result of this cloud of electrons, an alkene is an electron-rich molecule—it is a nucleophile. (Notice the relatively electron-rich pale orange area in the electrostatic potential maps for *cis*- and *trans*-2-butene.) We have also seen that a π bond is weaker than a σ bond (Section 1.14). The π bond, therefore, is the bond that is most easily broken when an alkene undergoes a reaction. For these reasons, we can predict that an alkene will react with an electrophile and, in the process, the π bond will break.

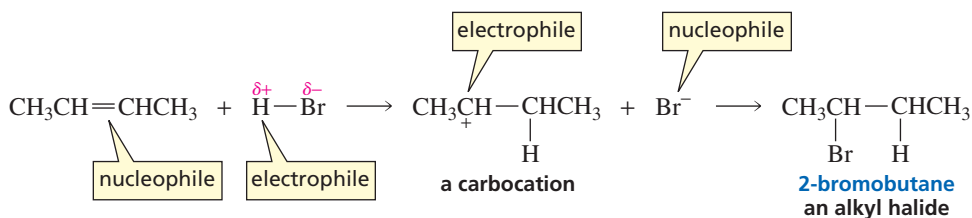
Thus, if a reagent such as hydrogen bromide is added to an alkene, the alkene (a nucleophile) will react with the partially positively charged hydrogen (an electrophile) of hydrogen bromide; the product of the reaction will be a carbocation. In the second step of the reaction, the positively charged carbocation (an electrophile) will react with the negatively charged bromide ion (a nucleophile) to form an alkyl halide.

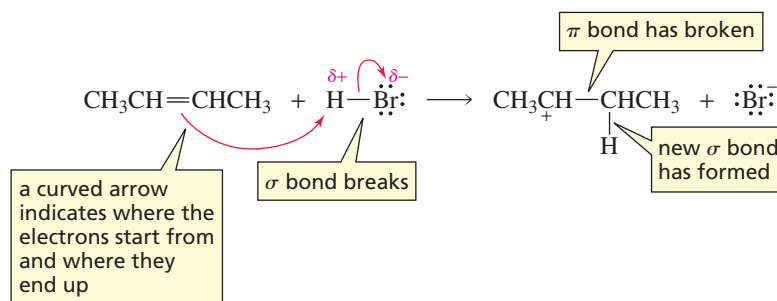
$$CH_3CH{=}CHCH_3 + \overset{\delta+}{H}{-}\overset{\delta-}{Br} \longrightarrow CH_3\overset{+}{C}H{-}CH(H)CH_3 + Br^- \longrightarrow CH_3CH(Br){-}CH(H)CH_3$$

nucleophile (alkene); electrophile (H of HBr); electrophile (carbocation); nucleophile (Br^-)

a carbocation

2-bromobutane
an alkyl halide

The mechanism of a reaction describes the step-by-step process by which reactants are changed into products.

The step-by-step description of the process by which reactants (in this case, alkene + HBr) are changed into products (an alkyl halide) is called the **mechanism of the reaction.** To help us understand a mechanism, curved arrows are drawn to show how the electrons move as new covalent bonds are formed and existing covalent bonds are broken. Each arrow represents the simultaneous movement of two electrons (an electron pair) from an electron-rich center (at the tail of the arrow) toward an electron-deficient center (at the point of the arrow). In this way, the arrows show which bonds are formed and which bonds are broken (Section 2.3).

For the reaction of 2-butene with HBr, an arrow is drawn to show that the two electrons of the π bond of the alkene are attracted to the partially positively charged hydrogen of HBr. The hydrogen is not immediately free to accept this pair of electrons because it is already bonded to a bromine, and hydrogen can be bonded to only one atom at a time (Section 1.4). Therefore, as the π electrons of the alkene move toward the hydrogen, the H—Br bond breaks, with bromine keeping the bonding electrons. Notice that the π electrons are pulled away from one sp^2 carbon, but remain attached to the other. Thus, the two electrons that originally formed the π bond now form a new σ bond between carbon and the hydrogen from HBr. The product is positively charged, because the sp^2 carbon that did not form the new bond with hydrogen no longer shares the electrons represented by the π bond.

Curved arrows show the movement of the electrons; they are always drawn from an electron-rich center to an electron-deficient center.

An arrowhead with two barbs signifies the movement of two electrons.

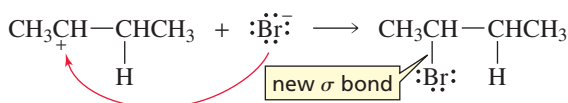
$$CH_3CH{=}CHCH_3 + \overset{\delta+}{H}{-}\overset{\delta-}{\ddot{B}r}\!: \longrightarrow CH_3\overset{+}{C}H{-}CH(H)CH_3 + :\ddot{B}r:^-$$

a curved arrow indicates where the electrons start from and where they end up

σ bond breaks

π bond has broken

new σ bond has formed

In the second step of the reaction, a lone pair on the negatively charged bromide ion forms a bond with the positively charged carbon of the carbocation. Notice that in both steps of the reaction, *a nucleophile reacts with an electrophile.*

A curved arrow indicates where the electrons start from and where they end up.

$$CH_3\overset{+}{C}H{-}CH(H)CH_3 + :\ddot{B}r:^- \longrightarrow CH_3CH(:\ddot{B}r:){-}CH(H)CH_3$$

new σ bond

Solely from the knowledge that a nucleophile reacts with an electrophile and a π bond is the weakest bond in an alkene, we have been able to predict that the product of the reaction of 2-butene and HBr is 2-bromobutane. The overall reaction involves the addition of 1 mole of HBr to 1 mole of the alkene. The reaction, therefore, is called an **addition reaction.** Because the first step of the reaction is the addition of an electrophile (H^+) to the alkene, the reaction is more precisely called an **electrophilic addition reaction.**

Electrophilic addition reactions are the characteristic reactions of alkenes.

At this point, you may think it would be easier just to memorize the fact that 2-bromobutane is the product of the reaction, without trying to understand the mechanism that explains why 2-bromobutane is the product. However, you will soon be encountering a great many reactions, and you will not be able to memorize them all. *It will be a lot easier to learn a few mechanisms that are based on similar rules than to try to memorize thousands of reactions.* And if you understand the mechanism of each reaction, the unifying principles of organic chemistry will soon be clear to you, making mastery of the material much easier and a lot more fun.

Alkenes undergo electrophilic addition reactions.

PROBLEM 4♦

Which of the following are electrophiles, and which are nucleophiles?

H^- CH_3O^- $CH_3C{\equiv}CH$ $CH_3\overset{+}{C}HCH_3$ NH_3

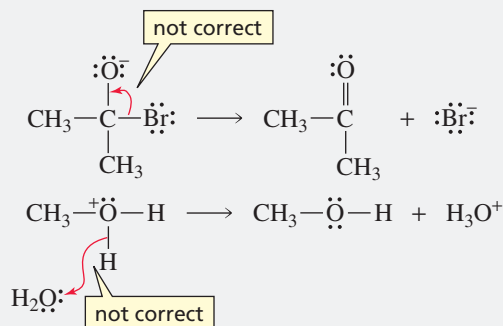
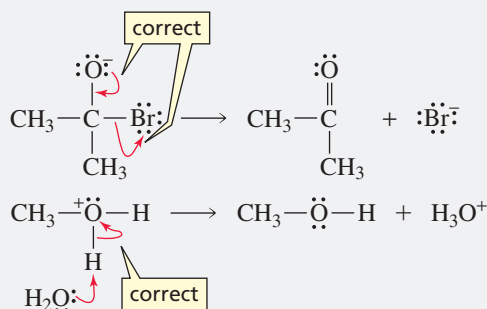
A Few Words About Curved Arrows

1. An arrow is used to show both the bond that forms and the bond that breaks. Draw the arrows so that they point in the direction of the electron flow; the arrows should never go against the flow. This means that *an arrow will point away from a negatively charged atom or toward a positively charged atom.*

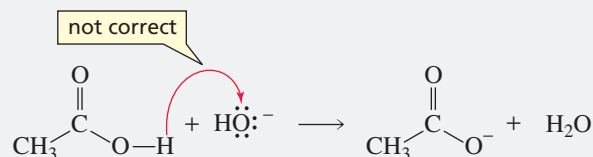
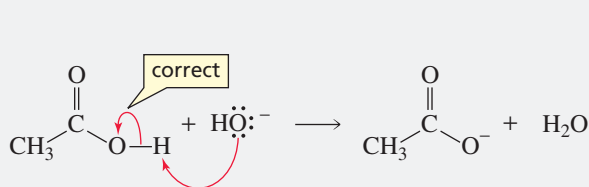
correct: $CH_3-C(O^-)(CH_3)-Br \longrightarrow CH_3-C(=O)-CH_3 + Br^-$

not correct: $CH_3-C(O^-)(CH_3)-Br \longrightarrow CH_3-C(=O)-CH_3 + Br^-$

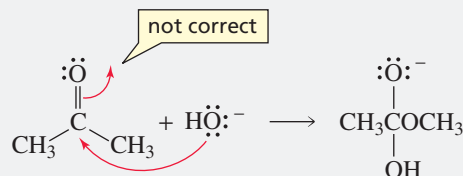
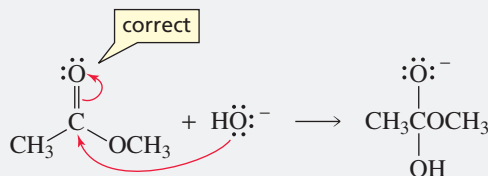
correct: $CH_3-\overset{+}{O}(H)-H + H_2O \longrightarrow CH_3-O-H + H_3O^+$

not correct: $CH_3-\overset{+}{O}(H)-H + H_2O \longrightarrow CH_3-O-H + H_3O^+$

2. Curved arrows are meant to indicate the movement of electrons. *Never use a curved arrow to indicate the movement of an atom.*

correct: $CH_3C(=O)O-H + HO^- \longrightarrow CH_3C(=O)O^- + H_2O$

not correct: $CH_3C(=O)O-H + HO^- \longrightarrow CH_3C(=O)O^- + H_2O$

3. *The head of a curved arrow always points at an atom or at a bond.* Never draw the head of the arrow pointing out into space.

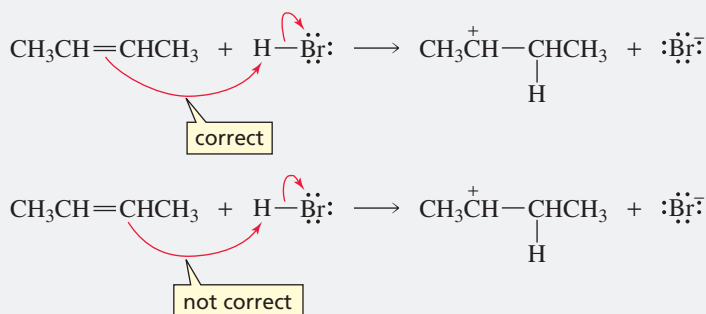
correct: $CH_3C(=O)OCH_3 + HO^- \longrightarrow CH_3C(O^-)(OH)OCH_3$

not correct: $CH_3C(=O)CH_3 + HO^- \longrightarrow CH_3C(O^-)(OH)CH_3$

4. *A curved arrow starts at an electron source; it does not start at an atom.* In the following example, the arrow starts at the electron-rich π bond, not at a carbon atom:

$$CH_3CH{=}CHCH_3 + H{-}\ddot{\underset{..}{Br}}: \longrightarrow CH_3\overset{+}{C}H{-}CH(H)CH_3 + :\ddot{\underset{..}{Br}}:^-$$

correct

$$CH_3CH{=}CHCH_3 + H{-}\ddot{\underset{..}{Br}}: \longrightarrow CH_3\overset{+}{C}H{-}CH(H)CH_3 + :\ddot{\underset{..}{Br}}:^-$$

not correct

PROBLEM 5

Draw the consequence of following the incorrect arrows in Part 1 of the box on page 183, "A Few Words About Curved Arrows." What is wrong with the structures that you obtain?

PROBLEM 6 Solved

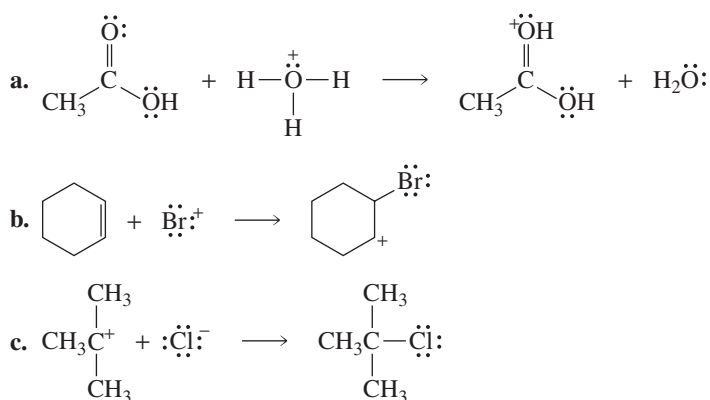
Use curved arrows to show the movement of electrons in each of the following reaction steps. (*Hint:* Look at the reactants and look at the products, and then draw the arrows to convert the reactants into products.)

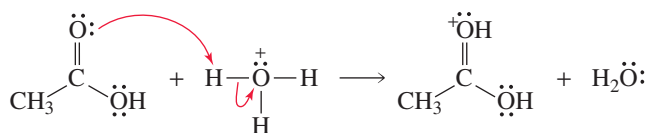
a. $CH_3C(=\ddot{O}:)\ddot{O}H + H{-}\overset{+}{\ddot{O}}{-}H(H) \longrightarrow CH_3C(={}^{+}\ddot{O}H)\ddot{O}H + H_2\ddot{O}:$

b. cyclohexene $+ \ :\ddot{Br}:^+ \longrightarrow$ cyclohexyl cation with $:\ddot{Br}:$ (positive charge on adjacent carbon)

c. $CH_3\overset{+}{C}(CH_3)_2 + :\ddot{Cl}:^- \longrightarrow CH_3C(CH_3)_2{-}\ddot{Cl}:$

NOTE TO THE STUDENT

It is critically important that you learn how to draw curved arrows. Be sure to do the tutorial on page 202. It should take no more than 15 minutes, yet it can make an enormous difference to your success in this course.

Solution to 6a The double-bonded oxygen gains a proton; H_3O^+ loses a proton with oxygen retaining the electrons it shared with the proton. Notice that the oxygen that gained a proton became positively charged, and the oxygen that lost a proton is no longer charged.

$$CH_3C(=\ddot{O}:)\ddot{O}H + H{-}\overset{+}{\ddot{O}}{-}H(H) \longrightarrow CH_3C(={}^{+}\ddot{O}H)\ddot{O}H + H_2\ddot{O}:$$

PROBLEM 7

For each of the reactions in Problem 6, indicate which reactant is the nucleophile and which is the electrophile.

A Reaction Coordinate Diagram Describes the Energy Changes that Take Place During a Reaction

The mechanism of a reaction, as we have shown on page 182, describes the steps known to occur as reactants are converted into products. A **reaction coordinate diagram** shows the energy changes that take place in each of these steps.

In a reaction coordinate diagram, the total energy of all species is plotted against the progress of the reaction. A reaction progresses from left to right as written in a chemical equation, so the energy of the reactants is plotted on the left-hand side of the *x*-axis, and the energy of the products is plotted on the right-hand side. A typical reaction coordinate diagram is shown in Figure 5.1. It describes the reaction of A—B with C to form A and B—C. Remember that *the more stable the species, the lower its energy.*

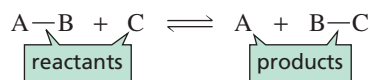
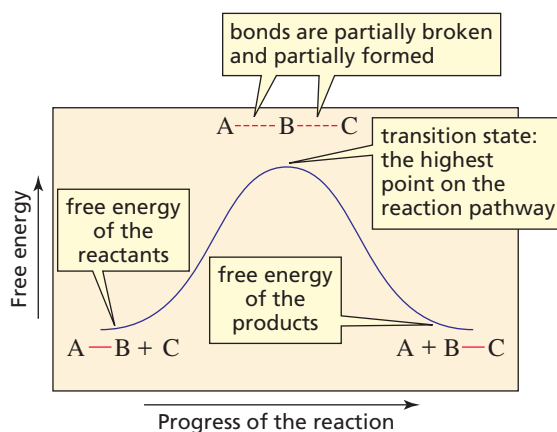
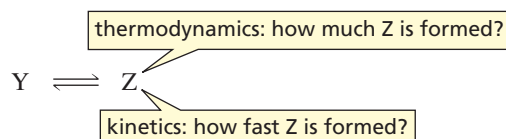
$$\underbrace{A{-}B + C}_{\text{reactants}} \rightleftharpoons \underbrace{A + B{-}C}_{\text{products}}$$

As the reactants are converted into products, the reaction passes through a *maximum* energy state called a **transition state.** The structure of the transition state is between the structure of the reactants and the structure of the products. As reactants are converted to products, bonds that break and bonds that form are partially broken and partially formed in the transition state. (Dashed lines are used to show partially broken or partially formed bonds.) The height of the transition state (the difference between the energy of the reactants and the energy of the transition state) tells us how likely it is that the reaction will occur; if the height is too great, the reactants will not be able to be converted into products, so no reaction will take place.

The more stable the species, the lower its energy.

Figure 5.1 A reaction coordinate diagram, which shows the energy changes that take place as the reaction progresses from reactants to products. The dashed lines in the transition state indicate bonds that are partially formed or partially broken.

5.4 THERMODYNAMICS: HOW MUCH PRODUCT IS FORMED?

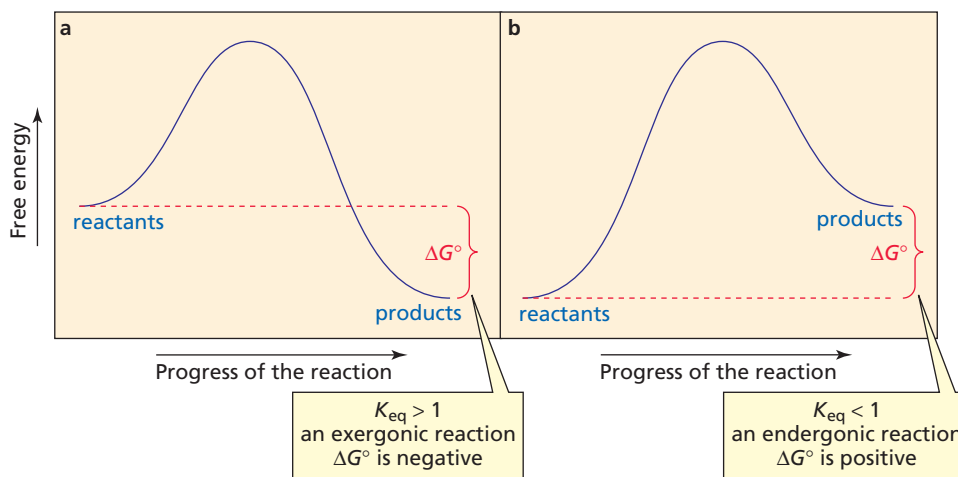
To understand the energy changes that take place in a reaction such as the addition of HBr to an alkene, you need to understand some of the basic concepts of *thermodynamics*, which describes a reaction at equilibrium, and *kinetics*, which explains the rates of chemical reactions.

Consider a reaction in which Y is converted to Z: the *thermodynamics* of the reaction tells us the relative amounts of reactants (Y) and products (Z) present when the reaction has reached equilibrium, whereas the *kinetics* of the reaction tells us how fast Y is converted into Z.

Thermodynamics describes the properties of a system at equilibrium. The relative concentrations of reactants and products at equilibrium can be expressed by an equilibrium constant, K_{eq}.

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{C} + \mathrm{D}$$

$$K_{eq} = \frac{[\text{products}]}{[\text{reactants}]} = \frac{[\mathrm{C}][\mathrm{D}]}{[\mathrm{A}][\mathrm{B}]}$$

A reaction is over when the system reaches equilibrium. The relative concentrations of products and reactants at equilibrium depend on their relative stabilities: *the more stable the compound, the greater its concentration at equilibrium.* Thus, if the products are more stable (have a lower free energy) than the reactants (Figure 5.2a), there will be a higher concentration of products than reactants at equilibrium, and K_{eq} will be greater than 1. On the other hand, if the reactants are more stable than the products (Figure 5.2b), there will be a higher concentration of reactants than products at equilibrium, and K_{eq} will be less than 1. A reaction that leads to a higher concentration of products compared with the concentration of reactants is called a **favorable reaction.**

Figure 5.2
Reaction coordinate diagrams for
(a) a reaction in which the products are more stable than the reactants (an exergonic reaction) and
(b) a reaction in which the products are less stable than the reactants (an endergonic reaction).

Now you can understand why the strength of an acid is determined by the stability of its conjugate base (Section 2.6)—as the base becomes more stable, the equilibrium constant (K_a) for its formation becomes larger, and the larger the K_a, the stronger the acid.

The difference between the free energy of the products and the free energy of the reactants under standard conditions is called the **Gibbs free-energy change,** or ΔG°. The symbol ° indicates standard conditions, which means that all species are at a concentration of 1 M, a temperature of 25 °C, and a pressure of 1 atm.

$$\Delta G^\circ = \textbf{free energy of the products} - \textbf{free energy of the reactants}$$

From this equation, we can see that ΔG° will be negative if the products have a lower free energy (are more stable) than the reactants. In other words, the reaction will release more energy than it consumes; such a reaction is called an **exergonic reaction** (Figure 5.2a).

If the products have a higher free energy (are less stable) than the reactants, ΔG° will be positive, and the reaction will consume more energy than it releases; such a reaction is called an **endergonic reaction** (Figure 5.2b).

The more stable the compound, the greater its concentration at equilibrium.

When products are favored at equilibrium, ΔG° is negative and K_{eq} is greater than 1.

When reactants are favored at equilibrium, ΔG° is positive and K_{eq} is less than 1.

We have just seen that whether reactants or products are favored at equilibrium can be indicated by the equilibrium constant (K_{eq}) or by the change in free energy (ΔG°). These two quantities are related by the equation

$$\Delta G^\circ = -RT \ln K_{eq}$$

where R is the gas constant (1.986×10^{-3} kcal mol^{-1} K^{-1} or 8.341×10^{-3} kJ mol^{-1} K^{-1})* and T is the temperature in kelvins. (The Kelvin scale avoids negative temperatures by assigning 0 K to −273 °C, the lowest temperature known. Thus, because K = °C + 273, 25 °C = 298 K.)

*1 kcal = 4.184 kJ

William Thomson (1824–1907) was born in Belfast, Northern Ireland. He was a professor of natural philosophy at the University of Glasgow, Scotland. For developing the Kelvin scale of absolute temperature and other important work in mathematical physics, he was given the title Baron Kelvin, which allowed him to be called ***Lord Kelvin.*** The name comes from the river Kelvin that flows by the University of Glasgow (see page 176). His statue is in the botanic gardens that are adjacent to The Queen's University of Belfast.

The Gibbs standard free-energy change ($G°$) has an enthalpy ($H°$) component and an entropy ($\Delta S°$) component (T is the temperature in degrees kelvin):

$$\Delta G° = \Delta H° - T\Delta S°$$

The **enthalpy** term ($\Delta H°$) is the heat given off or the heat consumed during the course of a reaction. Heat is given off when bonds are formed, and heat is consumed when bonds are broken. Thus, $\Delta H°$ is a measure of the energy of the bond-making and bond-breaking processes that occur as reactants are converted into products.

$$\Delta H° = \textbf{heat required to break bonds} - \textbf{heat released from breaking bonds}$$

If the bonds that are formed in a reaction are stronger than the bonds that are broken, more energy will be released in the bond-forming process than will be consumed in the bond-breaking process, and $\Delta H°$ will be negative. A reaction with a negative $\Delta H°$ is called an **exothermic reaction.** If the bonds that are formed are weaker than those that are broken, $\Delta H°$ will be positive. A reaction with a positive $\Delta H°$ is called an **endothermic reaction.**

Entropy ($\Delta S°$) is a measure of the freedom of motion in a system. Restricting the freedom of motion of a molecule decreases its entropy. For example, in a reaction in which two molecules come together to form a single molecule, the entropy of the product will be less than the entropy of the reactants because two separate molecules can move in ways that are not possible when they are bound together in a single molecule. In such a reaction, $\Delta S°$ will be negative. In a reaction in which a single molecule is cleaved into two separate molecules, the products will have greater freedom of motion than the reactant, and $\Delta S°$ will be positive.

Entropy is a measure of the freedom of motion in a system.

$$\Delta S° = \textbf{freedom of motion of the products} - \textbf{freedom of motion of the reactants}$$

PROBLEM 8

a. For which reaction in each set below will $\Delta S°$ be more significant?
b. For which reaction will $\Delta S°$ be positive?

1. $A \rightleftharpoons B$ or $A + B \rightleftharpoons C$
2. $A + B \rightleftharpoons C$ or $A + B \rightleftharpoons C + D$

We have seen that a favorable reaction has a negative $\Delta G°$ (and a $K_{eq} > 1$). If you examine the expression for the Gibbs standard free-energy change, you will find that negative values of $\Delta H°$ and positive values of $\Delta S°$ contribute to make $\Delta G°$ negative. In other words, *the formation of products with stronger bonds and greater freedom of motion causes $\Delta G°$ to be negative* and, therefore, the reaction to be a favorable one.

The formation of products with stronger bonds and greater freedom of motion causes $\Delta G°$ to be negative.

5.5 INCREASING THE AMOUNT OF PRODUCT FORMED IN A REACTION

Fortunately, there are ways to increase the amount of product formed in a reaction.

Le Châtelier's principle states that *if an equilibrium is disturbed, then the system will adjust to offset the disturbance.* In other words, if the concentration of C or D is decreased, then A and B will react to form more C and D in order to maintain the value of the equilibrium constant. (The value of a constant must be maintained—that is why it is called a *constant*.)

If an equilibrium is disturbed, the system will adjust to offset the disturbance.

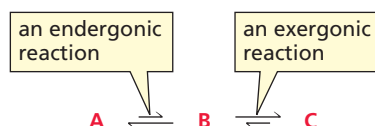
$$\mathbf{A + B \rightleftharpoons C + D}$$

$$K_{eq} = \frac{[\mathrm{C}][\mathrm{D}]}{[\mathrm{A}][\mathrm{B}]}$$

Thus, if a product crystallizes out of solution as it is formed, or if it can be distilled off as a liquid or driven off as a gas, the reactants will continue to react to replace the departing product in order to maintain the relative concentrations of products and

reactants (that is, to maintain the value of the equilibrium constant). Additional product can also be formed if the equilibrium is disturbed by increasing the concentration of one or more of the reactants.

Living organisms obtain energy by carrying out a series of sequential reactions that convert complex nutrient molecules (such as glucose) into simple molecules (Section 19.0). Such a series of reactions is called a **metabolic pathway.** Some of the reactions in a metabolic pathway are endergonic and therefore produce very little product. However, the amount of product produced is increased if the endergonic reaction is followed by a highly exergonic reaction—another application of Le Châtelier's principle.

For example, very little B is produced in the first of the two sequential reactions shown here, because the conversion of A to B is endergonic. However, as the highly exergonic second reaction converts B to C, the first reaction will replenish the equilibrium concentration of B. Thus, the exergonic reaction drives the endergonic reaction that precedes it.

The two reactions (an endergonic reaction followed by an exergonic reaction) are called **coupled reactions.** Coupled reactions are the thermodynamic basis for how metabolic pathways are regulated since they are composed of both endergonic and exergonic reactions.

5.6 USING ΔH° VALUES TO DETERMINE THE RELATIVE STABILITIES OF ALKENES

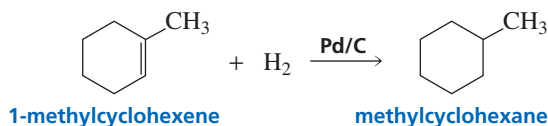
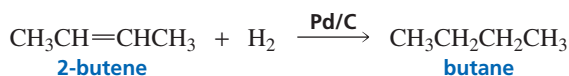
Hydrogen (H_2) adds to the double bond of an alkene, in the presence of a metal catalyst, to form an alkane. The most common metal catalyst is palladium, which is used as a powder adsorbed on charcoal to maximize its surface area; it is referred to as "palladium on carbon" and is abbreviated as Pd/C. The metal catalyst is required to weaken the very strong H—H bond. (See Figure 1.2 on page 47.)

The addition of hydrogen to a compound is a reduction reaction. A **reduction reaction** increases the number of C—H bonds.

A reduction reaction increases the number of C—H bonds.

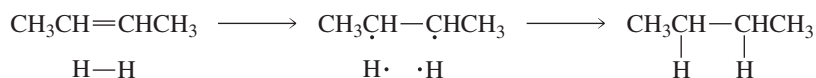
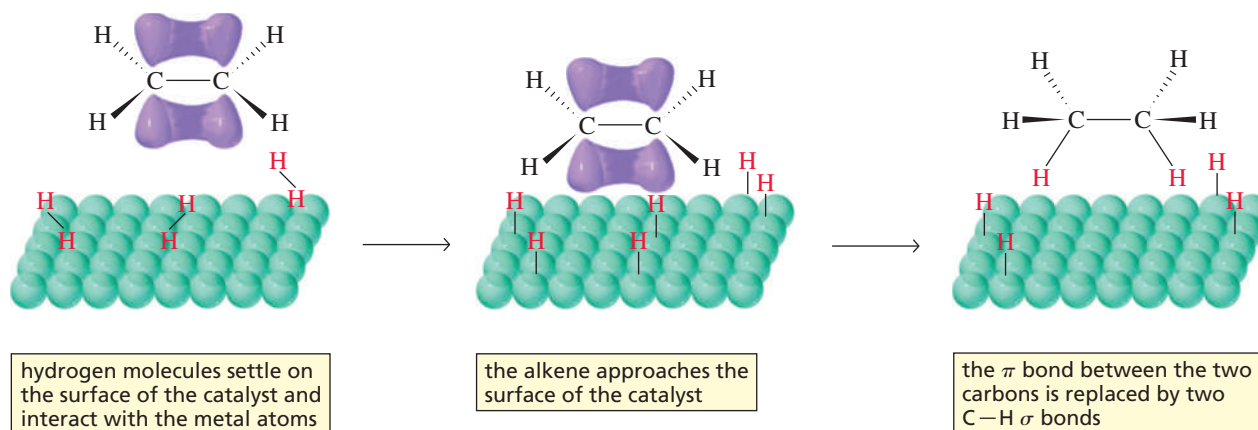
$$CH_3CH{=}CHCH_3 + H_2 \xrightarrow{Pd/C} CH_3CH_2CH_2CH_3$$

2-butene → butane

1-methylcyclohexene $+ H_2 \xrightarrow{Pd/C}$ methylcyclohexane

The addition of hydrogen is called **hydrogenation.** Because hydrogenation reactions require a catalyst, they are called **catalytic hydrogenations.**

The mechanism for catalytic hydrogenation is too complex to be easily described. We know that hydrogen is adsorbed on the surface of the metal and that the alkene complexes with the metal by overlapping its *p* orbitals with the vacant orbitals of the metal. All the bond-breaking and bond-forming events occur on the surface of the metal. As the alkane product forms, it diffuses away from the metal surface. (See Figure 5.3.)

We can think of catalytic hydrogenation as occurring in the following way: both the H—H bond of H_2 and the π bond of the alkene break, and then the resulting hydrogen radicals add to the resulting carbon radicals.

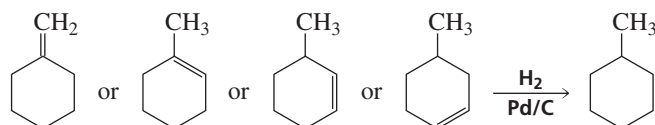
$$\underset{\text{H—H}}{CH_3CH{=}CHCH_3} \longrightarrow \underset{\text{H}\cdot\ \ \cdot\text{H}}{CH_3\dot{C}H{-}\dot{C}HCH_3} \longrightarrow \underset{\text{H}\ \ \ \ \text{H}}{CH_3CH{-}CHCH_3}$$

▲ **Figure 5.3** Catalytic hydrogenation of an alkene to form an alkane.

PROBLEM-SOLVING STRATEGY

Choosing the Reactant for a Synthesis

What alkene would you start with if you wanted to synthesize methylcyclohexane?

You need to choose an alkene with the same number of carbons as the desired product, attached in the same way as those in the desired product. Several alkenes could be used for this synthesis, because the double bond can be located anywhere in the molecule.

CH_2 (methylenecyclohexane) or CH_3 (1-methylcyclohexene) or CH_3 (3-methylcyclohexene) or CH_3 (4-methylcyclohexene) $\xrightarrow[\text{Pd/C}]{H_2}$ CH_3 (methylcyclohexane)

Now use the strategy you have just learned to solve Problem 9.

PROBLEM 9

What alkene would you start with if you wanted to synthesize

a. pentane? **b.** ethylcyclopentane?

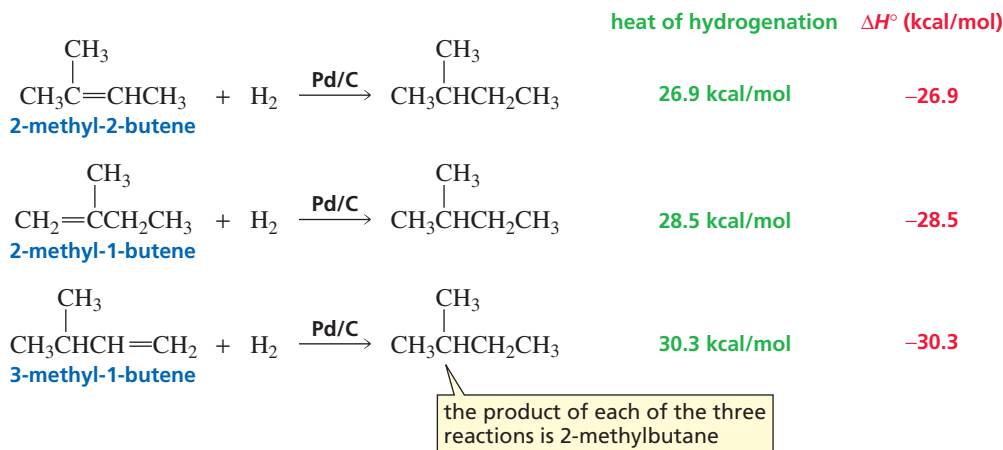
PROBLEM 10

How many different alkenes can be hydrogenated to form

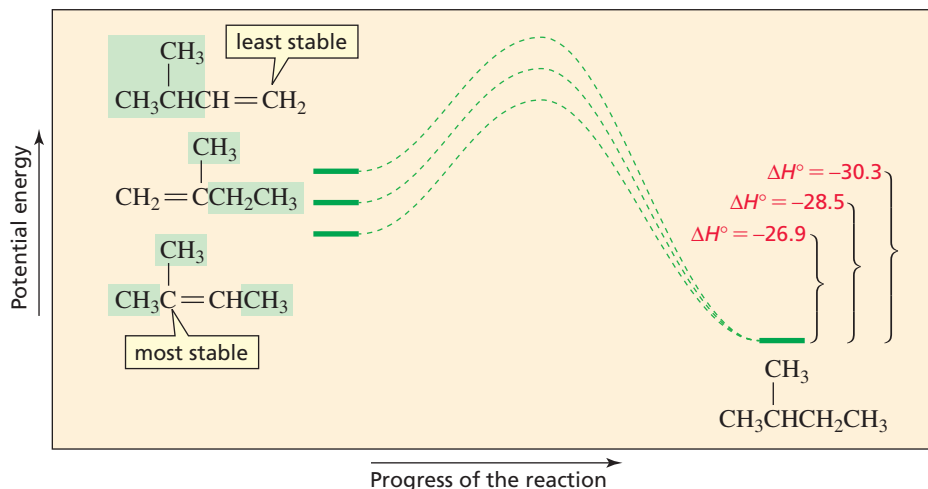
a. butane? **b.** 3-methylpentane? **c.** hexane?

To determine the relative stabilities of alkenes, the three hydrogenation reactions shown here were carried out and their $\Delta H°$ values were experimentally determined.

Reaction	heat of hydrogenation	$\Delta H°$ (kcal/mol)
$CH_3C(CH_3){=}CHCH_3 + H_2 \xrightarrow{\text{Pd/C}} CH_3CH(CH_3)CH_2CH_3$ (2-methyl-2-butene)	26.9 kcal/mol	–26.9
$CH_2{=}C(CH_3)CH_2CH_3 + H_2 \xrightarrow{\text{Pd/C}} CH_3CH(CH_3)CH_2CH_3$ (2-methyl-1-butene)	28.5 kcal/mol	–28.5
$CH_3CH(CH_3)CH{=}CH_2 + H_2 \xrightarrow{\text{Pd/C}} CH_3CH(CH_3)CH_2CH_3$ (3-methyl-1-butene)	30.3 kcal/mol	–30.3

the product of each of the three reactions is 2-methylbutane

The heat released in a hydrogenation reaction is called the **heat of hydrogenation.** It is customary to give it a positive value. Hydrogenation reactions, however, are exothermic (they have negative $\Delta H°$ values), so *the heat of hydrogenation is the value of* $\Delta H°$ *without the negative sign.*

The $\Delta H°$ values tell us the relative energies of the reactants and products for the three catalytic hydrogenation reactions. However, because we do not know the precise mechanism of the reaction, we cannot draw reaction coordinate diagrams for the reactions. So we will connect the energy of the reactants and products with dotted lines to indicate the uncertainty of the energy change that occurs between the reactants and products (Figure 5.4).

Figure 5.4
The relative energies (stabilities) of three alkenes that can be catalytically hydrogenated to 2-methylbutane. The most stable alkene has the smallest heat of hydrogenation. (Notice that when a reaction coordinate diagram shows $\Delta H°$ values, the *y*-axis is potential energy; when it shows $\Delta G°$ values, the *y*-axis is free energy [Figure 5.2].)

The three reactions all form the same alkane product, so the energy of the *product* in Figure 5.4 is the same for each reaction. The three reactions, however, have different heats of hydrogenation, so the three *reactants* must have different energies. For example, 3-methyl-1-butene releases the most heat, so it must have the most energy to begin with (it must be the *least* stable of the three alkenes). In contrast, 2-methyl-2-butene releases the least heat, so it must have the least energy to begin with (it must be the *most* stable of the three alkenes). Notice that *the most stable alkene has the smallest heat of hydrogenation.*

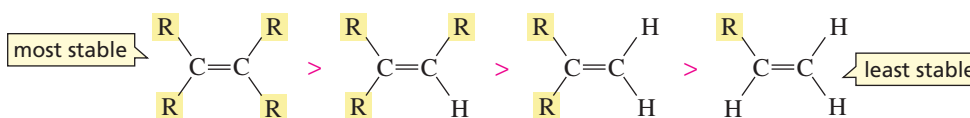
The most stable alkene has the smallest heat of hydrogenation.

If you look at the structures of the three alkene reactants in Figure 5.4, you will see that the stability of an alkene increases as the number of alkyl substituents bonded to the sp^2 carbons increases.

For example, the most stable alkene in Figure 5.4 has two alkyl substituents bonded to one sp^2 carbon and one alkyl substituent bonded to the other sp^2 carbon, for a total of three alkyl substituents (three methyl groups) bonded to its two sp^2 carbons. The alkene of intermediate stability has two alkyl substituents (a methyl group and an ethyl group) bonded to its sp^2 carbons, and the least stable of the three alkenes has only one alkyl substituent (an isopropyl group) bonded to an sp^2 carbon.

The more alkyl substituents bonded to the *sp*² carbons, the more stable the alkene.

relative stabilities of alkyl-substituted alkenes

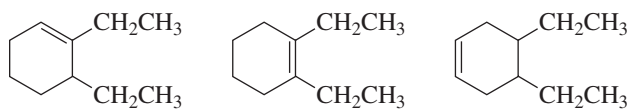
most stable $R_2C{=}CR_2 > R_2C{=}CHR > R_2C{=}CH_2 > RHC{=}CH_2$ least stable

We can therefore make the following statement: *the stability of an alkene increases as the number of alkyl substituents bonded to its* sp^2 *carbons increases.* (Some students like to remember this concept from the point of view of the hydrogens bonded to the sp^2 carbons—namely, *the stability of an alkene increases as the number of hydrogens bonded to its* sp^2 *carbons decreases.*)

PROBLEM 11♦

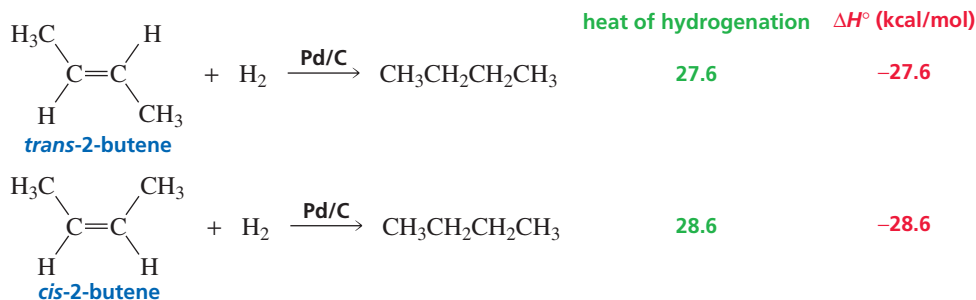
The same alkane is obtained from the catalytic hydrogenation of both alkene **A** and alkene **B.** The heat of hydrogenation of alkene **A** is 29.8 kcal/mol, and the heat of hydrogenation of alkene **B** is 31.4 kcal/mol. Which alkene is more stable?

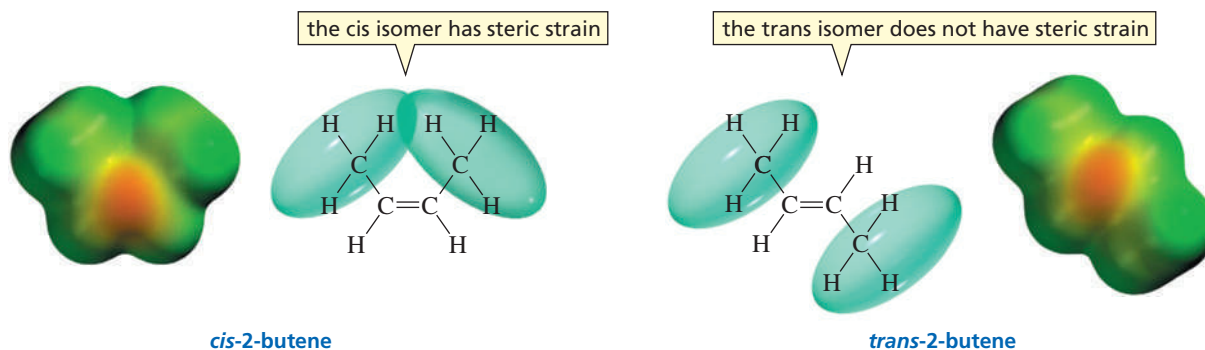
PROBLEM 12♦

a. Which of the following compounds is the most stable?

CH_2CH_3 / CH_2CH_3 (three cyclohexene isomers, each with two CH_2CH_3 substituents)

b. Which is the least stable?
c. Which has the smallest heat of hydrogenation?

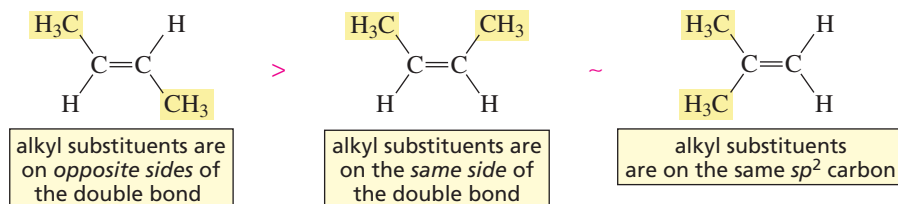
Both *trans*-2-butene and *cis*-2-butene have two alkyl substituents bonded to their sp^2 carbons, but *trans*-2-butene has a smaller heat of hydrogenation. This means that the trans isomer, in which the large substituents are farther apart, is more stable than the cis isomer.

	heat of hydrogenation	$\Delta H°$ (kcal/mol)
trans-2-butene + H_2 $\xrightarrow{Pd/C}$ $CH_3CH_2CH_2CH_3$	27.6	–27.6
cis-2-butene + H_2 $\xrightarrow{Pd/C}$ $CH_3CH_2CH_2CH_3$	28.6	–28.6

When large substituents are on the same side of the double bond, as in a cis isomer, their electron clouds can interfere with each other, causing steric strain in the molecule. Steric strain makes a compound less stable (Section 3.9). When the large substituents are on opposite sides of the double bond, as in a trans isomer, their electron clouds cannot interact, so there is no destabilizing steric strain.

cis-2-butene *trans*-2-butene

The heat of hydrogenation of *cis*-2-butene, in which the two alkyl substituents are on the *same side* of the double bond, is similar to that of 2-methylpropene, in which the two alkyl substituents are on the *same carbon.* The three dialkyl-substituted alkenes are all *less* stable than a trialkyl-substituted alkene, and they are all *more* stable than a monoalkyl-substituted alkene.

relative stabilities of dialkyl-substituted alkenes

trans-(H_3C)CH=CH(CH_3) > cis-(H_3C)CH=CH(CH_3) ~ (H_3C)$_2$C=CH_2

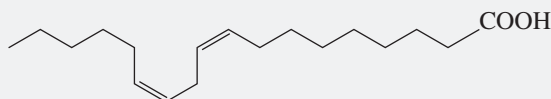
alkyl substituents are on *opposite sides* of the double bond | alkyl substituents are on the *same side* of the double bond | alkyl substituents are on the same sp^2 carbon

PROBLEM 13♦

Rank the following compounds in order from most stable to least stable:

trans-3-hexene, *cis*-3-hexene, *cis*-2,5-dimethyl-3-hexene, *cis*-3,4-dimethyl-3-hexene

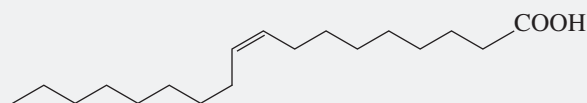
Trans Fats

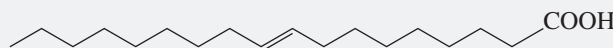
Oils are liquids at room temperature because their fatty acid components contain several carbon–carbon double bonds, which makes it difficult for them to pack closely together. In contrast, the fatty acid components of fats have fewer double bonds, so they can pack together more closely (Section 11.12). Because of their many double bonds, oils are said to be polyunsaturated.

COOH

linoleic acid
an 18-carbon fatty acid with two cis double bonds

Some or all of the double bonds in oils can be reduced by catalytic hydrogenation. For example, margarine and shortening are prepared by hydrogenating vegetable oils, such as soybean oil and safflower oil, until they have the desired creamy, solid consistency of butter.

All the double bonds in naturally occurring fats and oils have the cis configuration. The catalyst used in the hydrogenation process also catalyzes cis–trans isomerization, forming what is known as a trans fat (Section 4.1).

COOH

oleic acid
an 18-carbon fatty acid with one cis double bond
before being heated

COOH

elaidic acid
an 18-carbon fatty acid with one trans double bond
after being heated

Trans fats are a health concern because they increase LDL, the so-called "bad" cholesterol (Section 3.14). Epidemiological studies have shown that an increase in the daily intake of trans fats significantly increases the incidence of cardiovascular disease.

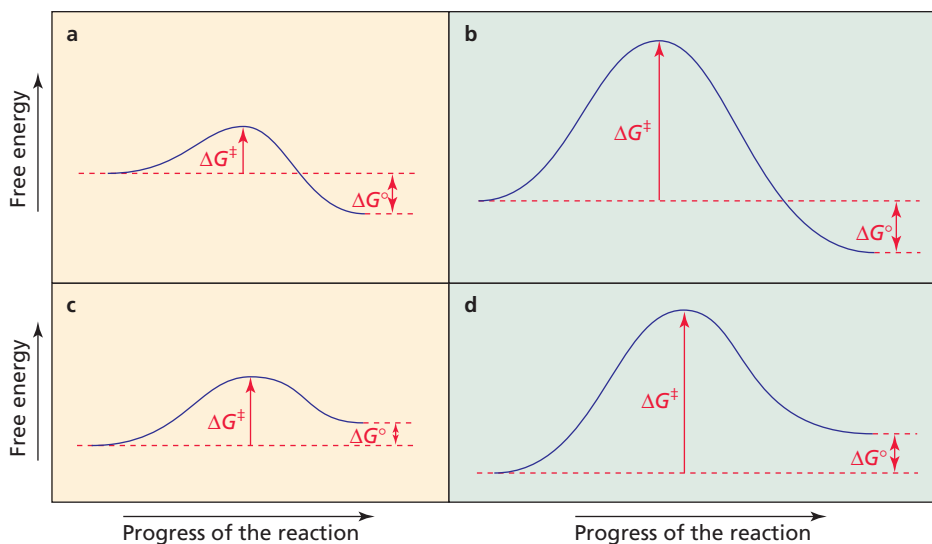
5.7 KINETICS: HOW FAST IS THE PRODUCT FORMED?

Knowing that a reaction is exergonic will not tell you how fast the reaction occurs, because ΔG° describes only the difference between the stability of the reactants and the stability of the products. It does not indicate anything about the energy barrier of the reaction, which is the energy "hill" that has to be climbed for the reactants to be converted into products. **Kinetics** is the field of chemistry that studies the rates of chemical reactions and the factors that affect those rates.

The energy barrier of a reaction (indicated in Figure 5.5 by $\Delta G^\ddagger$) is called the **free energy of activation.** It is the difference between the free energy of the transition state and the free energy of the reactants:

$$\Delta G^\ddagger = \textbf{free energy of the transition state} - \textbf{free energy of the reactants}$$

As $\Delta G^\ddagger$ decreases, the rate of the reaction increases. Thus, *anything that makes the reactants less stable or makes the transition state more stable will make the reaction go faster.*

How easy it is to reach the transition state is indicted by a **rate constant.** A fast reaction has a large rate constant; a slow reaction has a small rate constant.

The greater the energy barrier, the slower the reaction.

◀ **Figure 5.5**
Reaction coordinate diagrams (drawn on the same scale) for
(a) a fast exergonic reaction.
(b) a slow exergonic reaction.
(c) a fast endergonic reaction.
(d) a slow endergonic reaction.

Some exergonic reactions have small free energies of activation (large rate constants) and therefore can take place at room temperature (Figure 5.5a). In contrast, some exergonic reactions have free energies of activation that are so large that the reaction cannot take place unless energy is supplied in addition to that provided by the existing thermal conditions (Figure 5.5b). Endergonic reactions can also have either small free energies of activation (large rate constants), as in Figure 5.5c, or large free energies of activation (small rate constants), as in Figure 5.5d.

Let's now look at the difference between thermodynamic stability and kinetic stability.

> **Thermodynamic stability** is indicated by ΔG°. If ΔG° is negative, then the product is *thermodynamically stable* compared with the reactant; if ΔG° is positive, then the product is *thermodynamically unstable* compared with the reactant.
>
> **Kinetic stability** is indicated by $\Delta G^{\ddagger}$. If $\Delta G^{\ddagger}$ is large, then the reactant is *kinetically stable* because it reacts slowly. If $\Delta G^{\ddagger}$ is small, then the reactant is *kinetically unstable*—it reacts rapidly. Similarly, if $\Delta G^{\ddagger}$ for the reverse reaction is large, then the product is kinetically stable, but if it is small, then the product is kinetically unstable.

The more stable the species, the lower its energy.

Generally, when chemists use the term *stability*, they are referring to thermodynamic stability.

PROBLEM 14♦

The rate constant for a reaction can be increased by ______ the stability of the reactant or by ______ the stability of the transition state.

PROBLEM 15♦

a. Which of the reactions in Figure 5.5 has a product that is thermodynamically stable compared with the reactant?
b. Which of the reactions in Figure 5.5 has the most kinetically stable product?
c. Which of the reactions in Figure 5.5 has the least kinetically stable product?

PROBLEM 16

Draw a reaction coordinate diagram for a reaction in which

a. the product is thermodynamically unstable and kinetically unstable.
b. the product is thermodynamically unstable and kinetically stable.

5.8 THE RATE OF A CHEMICAL REACTION

The rate of a chemical reaction is the speed at which the reacting substances are used up or the speed at which the products are formed. The rate of a reaction depends on the following factors:

1. **The number of collisions that take place between the reacting molecules in a given period of time.** The rate of the reaction increases as the number of collisions increases.
2. **The fraction of collisions that occur with sufficient energy to get the reacting molecules over the energy barrier.** If the free energy of activation is small, then more collisions will lead to reaction than if the free energy of activation is large.
3. **The fraction of collisions that occur with the proper orientation.** 2-Butene and HBr will react only if the molecules collide with the hydrogen of HBr approaching the π bond of 2-butene. If a collision occurs with the hydrogen approaching a methyl group of 2-butene, no reaction will take place, regardless of the energy of the collision.

$$\textbf{rate of a reaction} = \left(\begin{array}{c}\textbf{number of collisions}\\ \textbf{per unit of time}\end{array}\right) \times \left(\begin{array}{c}\textbf{fraction with}\\ \textbf{sufficient energy}\end{array}\right) \times \left(\begin{array}{c}\textbf{fraction with}\\ \textbf{proper orientation}\end{array}\right)$$

- Increasing the concentration of the reactants increases the rate of a reaction because it increases the number of collisions that occur in a given period of time.
- Increasing the temperature at which the reaction is carried out also increases the rate of a reaction because it increases the kinetic energy of the molecules, which increases both the frequency of collisions (molecules that are moving faster collide more frequently) and the number of collisions that have sufficient energy to get the reacting molecules over the energy barrier.
- The rate of a reaction can also be increased by a catalyst (Section 5.10).

5.9 THE REACTION COORDINATE DIAGRAM FOR THE REACTION OF 2-BUTENE WITH HBr

We have seen that the addition of HBr to 2-butene is a two-step process (Section 5.3). In each step, the reactants pass through a transition state as they are converted into products. The structure of the transition state for each of the steps is shown below in brackets.

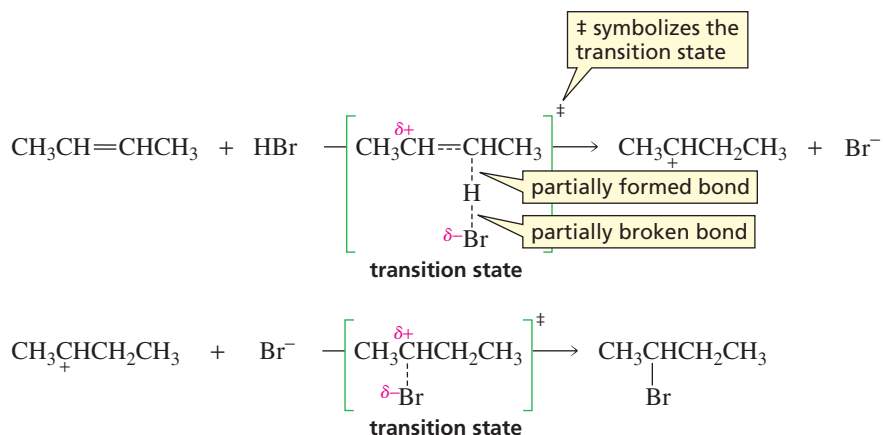
$$CH_3CH{=}CHCH_3 + HBr \longrightarrow \left[\begin{array}{c}CH_3\overset{\delta+}{C}H{\cdots}CHCH_3\\ \vdots\\ H\\ \vdots\\ \delta-Br\end{array}\right]^{\ddagger} \longrightarrow CH_3\underset{+}{C}HCH_2CH_3 + Br^-$$

transition state

‡ symbolizes the transition state

partially formed bond

partially broken bond

$$CH_3\underset{+}{C}HCH_2CH_3 + Br^- \longrightarrow \left[\begin{array}{c}CH_3\overset{\delta+}{C}HCH_2CH_3\\ \vdots\\ \delta-Br\end{array}\right]^{\ddagger} \longrightarrow \begin{array}{c}CH_3CHCH_2CH_3\\ |\\ Br\end{array}$$

transition state

Notice that the bonds that break and the bonds that form during the course of the reaction are partially broken and partially formed in the transition state, as indicated by dashed lines. Atoms that either become charged or lose their charge during the course of the

reaction are partially charged in the transition state. (Transition states are always shown in brackets with a double-dagger superscript.)

A reaction coordinate diagram (Section 5.3) can be drawn for each step of a reaction (Figure 5.6). In the first step of the addition reaction, the alkene is converted into a carbocation that is higher in energy (less stable) than the reactants. The first step, therefore, is endergonic ($\Delta G°$ is > 0). In the second step, the carbocation reacts with a nucleophile to form a product that is lower in energy (more stable) than the carbocation reactant. This step, therefore, is exergonic ($\Delta G°$ is < 0).

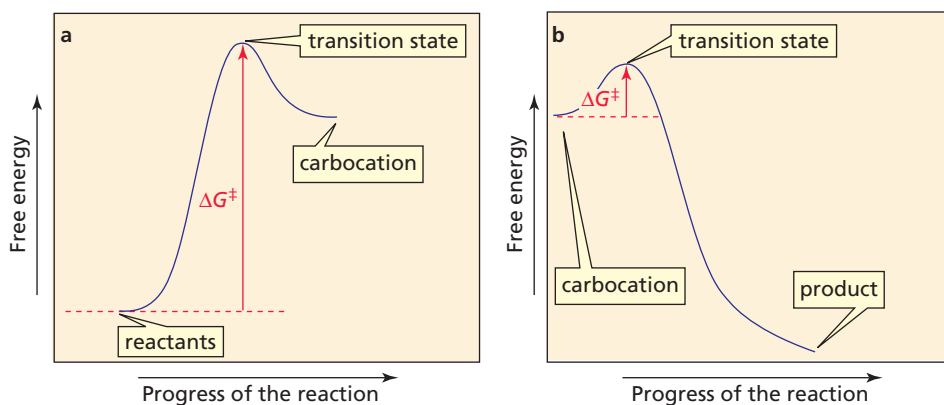



Figure 5.6
Reaction coordinate diagrams for the two steps in the addition of HBr to 2-butene:
(a) the first step (formation of the carbocation)
(b) the second step (formation of the alkyl halide)

Because the products of the first step are the reactants for the second step, we can hook the two reaction coordinate diagrams together to obtain the reaction coordinate diagram that describes the pathway for the overall reaction (Figure 5.7). The $\Delta G°$ for the overall reaction is the difference between the free energy of the final products and the free energy of the initial reactants. Figure 5.7 shows that the overall reaction is exergonic ($\Delta G°$ is negative).

A chemical species that is a product of one step of a reaction and a reactant for the next step is called an **intermediate.** The carbocation intermediate formed in this reaction is too unstable to be isolated, but some reactions have more stable intermediates that can be isolated. **Transition states,** in contrast, represent the highest-energy structures that are involved in the reaction. They exist only fleetingly and they can never be isolated (Figure 5.7).

Transition states have partially formed bonds. Intermediates have fully formed bonds.

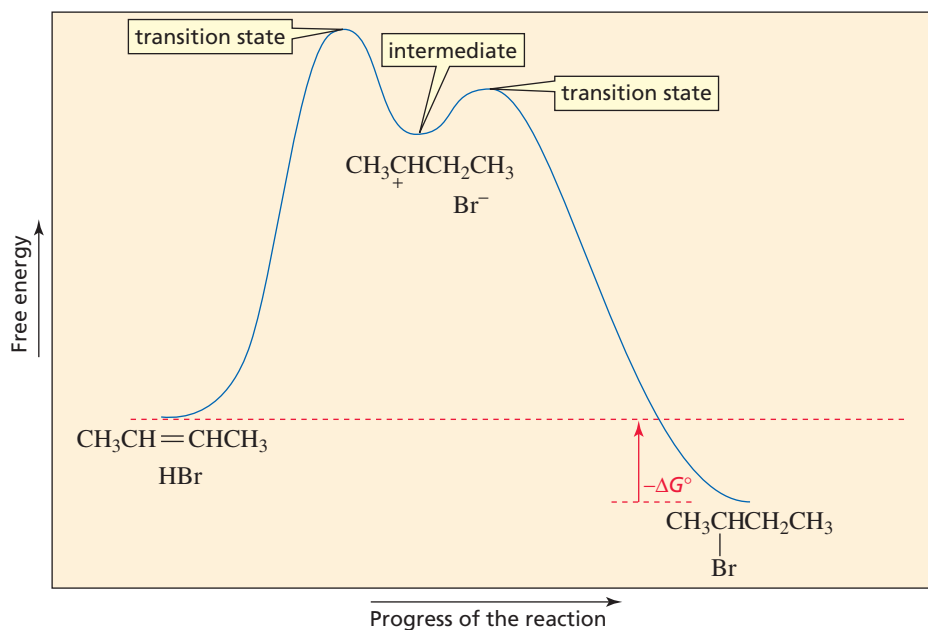



Figure 5.7
Reaction coordinate diagram for the addition of HBr to 2-butene to form 2-bromobutane.

Do not confuse transition states with intermediates. *Transition states have partially formed bonds, whereas intermediates have fully formed bonds.*

Figure 5.7 shows that the free energy of activation for the first step of the reaction is greater than the free energy of activation for the second step. In other words, the rate constant for the first step is smaller than the rate constant for the second step. This is what we would expect, since covalent bonds have to be broken in the first step, whereas no bonds are broken in the second step.

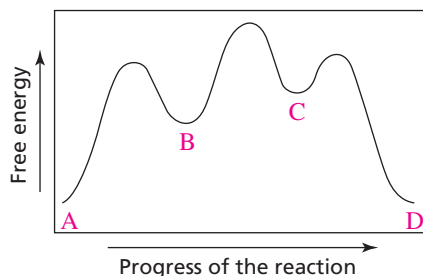
If a reaction has two or more steps, the step that has its transition state *at the highest point on the reaction coordinate* is called the **rate-determining step** or **rate-limiting step.** The rate-determining step controls the overall rate of the reaction. Thus, the rate-determining step for the reaction of 2-butene with HBr is the first step—the addition of the electrophile (the proton) to the alkene to form the carbocation.

Reaction coordinate diagrams can be used to explain why a given reaction forms a certain product and not others. We will see the first example of this use in Section 6.2.

PROBLEM 17

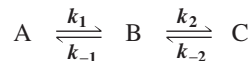
Draw a reaction coordinate diagram for a two-step reaction in which the first step is endergonic, the second step is exergonic, and the overall reaction is endergonic. Label the reactants, products, intermediates, and transition states.

PROBLEM 18♦

a. Which step in the reaction coordinate diagram has the greatest free energy of activation in the forward direction?

b. Is the first-formed intermediate more apt to revert to reactants or go on to form products?
c. Which step is the rate-determining step of the reaction?

PROBLEM 19♦

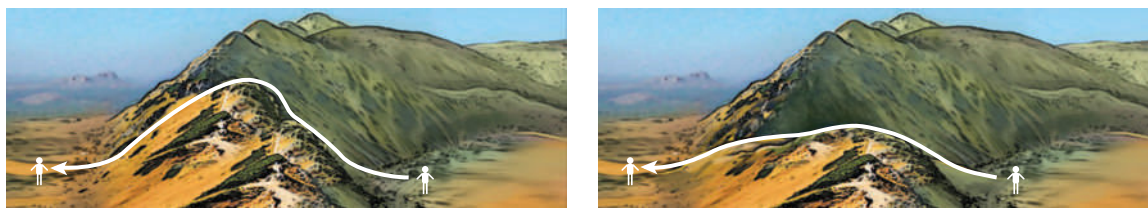
Draw a reaction coordinate diagram for the following reaction in which C is the most stable and B the least stable of the three species and the transition state going from A to B is more stable than the transition state going from B to C:

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{C}$$

a. How many intermediates are there?
b. How many transition states are there?
c. Which step has the greater rate constant in the forward direction?
d. Which step has the greater rate constant in the reverse direction?
e. Of the four steps, which has the greatest rate constant?
f. Which is the rate-determining step in the forward direction?
g. Which is the rate-determining step in the reverse direction?

5.10 CATALYSIS

A **catalyst** increases the rate of a reaction by giving the reactants a new pathway to follow—one with a smaller $\Delta G^{\ddagger}$. In other words, a catalyst decreases the energy barrier that has to be overcome in order to convert the reactants into products (Figure 5.8).

A catalyst gives the reactants a new pathway with a lower "energy hill."

If a catalyst is going to make a reaction go faster, it must participate in the reaction, but it is not consumed or changed during the reaction. Because the catalyst is not used up, only a small amount of it is needed to catalyze the reaction (typically, 1 to 10% of the

▲ **Figure 5.8**
A catalyst provides a pathway with a lower energy barrier but it does not change the energy of the starting point (the reactants) or the energy of the end point (the products).

number of moles of reactant). Notice in Figure 5.8 that the stability of the reactants and products is the same in both the catalyzed and uncatalyzed reactions. In other words, a catalyst does not change the relative concentrations of products and reactants when the system reaches equilibrium. Therefore, it does not change the *amount* of product formed; it changes only the *rate* at which it is formed.

A catalyst does not change the *amount* of product formed; it changes only the *rate* at which it is formed.

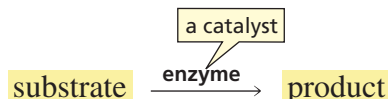
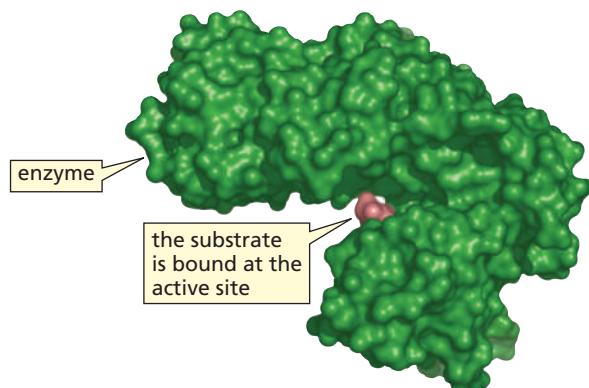
The most common catalysts are acids, bases, and nucleophiles. Acids catalyze a reaction by giving a proton to a reactant; bases catalyze a reaction by removing a proton from a reactant, and nucleophiles catalyze reactions by forming a new covalent bond with the reactant. We will see many examples of catalyzed reactions in the chapters that follow.

PROBLEM 20♦

Which of the following parameters would be different for a reaction carried out in the presence of a catalyst, compared with the same reaction carried out in the absence of a catalyst?

$$\Delta G°,\ \Delta H°,\ K_{eq},\ \Delta G^{\ddagger},\ \Delta S°$$

5.11 CATALYSIS BY ENZYMES

Essentially all reactions that occur in biological systems are reactions of organic compounds. These reactions almost always require a catalyst. Most biological catalysts are proteins called **enzymes.** Each biological reaction is catalyzed by a different enzyme.

The reactant of an enzyme-catalyzed reaction is called a **substrate.** The enzyme binds the substrate in a pocket of the enzyme called the **active site.** All the bond-making and bond-breaking steps of the reaction occur while the substrate is bound to the active site.

Unlike nonbiological catalysts, enzymes are specific for the substrate whose reaction they catalyze. All enzymes, however, do not have the same degree of specificity. Some are specific for a single compound and will not tolerate even the slightest variation in structure, whereas some catalyze the reaction of a family of compounds with related structures. The specificity of an enzyme for its substrate is an example of the phenomenon known as

molecular recognition—the ability of one molecule to recognize another molecule as a result of interactions between the molecules.

The specificity of an enzyme for its substrate results from the particular amino acid side chains that reside at the active site (Section 17.1). The side chains bind the substrate to the active site using hydrogen bonds, van der Waals forces, and dipole–dipole interactions—the same noncovalent interactions that hold molecules together (Section 3.7). A more in-depth discussion of the interaction between the enzyme and its substrate can be found in Chapter 18.

Cell walls consist of thousands of six-membered ring molecules linked by oxygen atoms. Lysozyme is an enzyme that cleaves bacterial cell walls by breaking the bond that holds the six-membered rings together. Figure 5.9 shows a portion of lysozyme's active site and some of the side chains that bind the substrate (the cell wall) in a precise location at the active site.

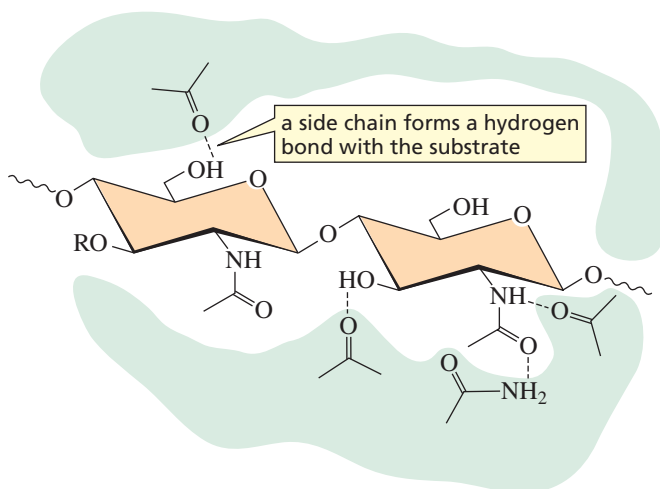



Figure 5.9
The side chains at the active site of the enzyme hold the substrate in the precise position necessary for reaction.

In addition to the side chains that bind the substrate to the active site, there are also side chains at the active site that are responsible for catalyzing the reaction. These side chains can be acids, bases, or nucleophiles—the same kinds of species that catalyze non-biological reactions (Section 5.10). For example, lysozyme has two catalytic groups at its active site, an acid catalyst and a nucleophilic catalyst (Figure 5.10). How these groups catalyze cleavage of the cell wall will be explained in Section 18.2, after you know more about the kinds of reactions that are involved.

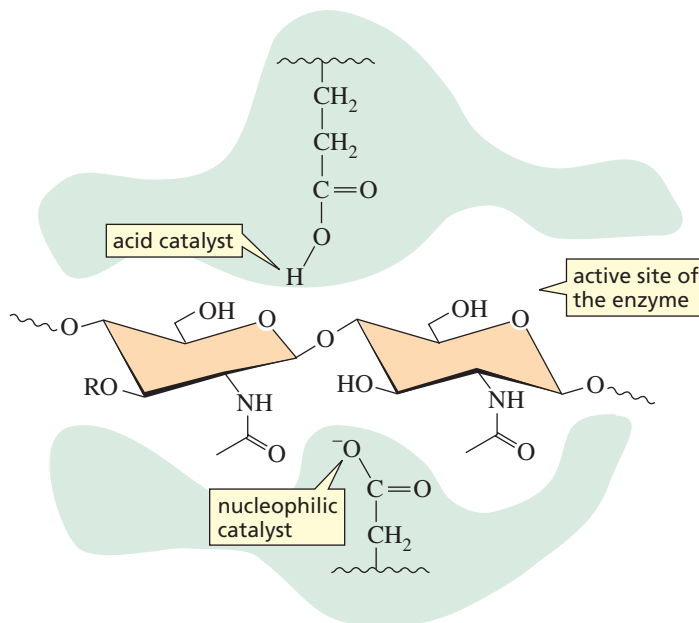



Figure 5.10
Two side chains at the active site of lysozyme are catalysts for the reaction that breaks the bond holding the six-membered rings together.

SOME IMPORTANT THINGS TO REMEMBER

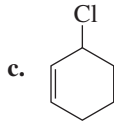
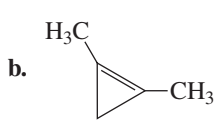
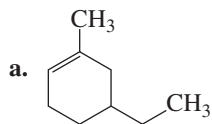
- An **alkene** is a hydrocarbon that contains a double bond. Because alkenes contain fewer than the maximum number of hydrogens, they are called **unsaturated hydrocarbons.**
- The double bond is the **functional group,** or center of reactivity, of an alkene.
- The **functional group suffix** of an alkene is "ene."
- When there are both a functional group suffix and a substituent, the functional group suffix gets the lowest possible number.
- All compounds with a particular **functional group** react in the same way.
- Because of the cloud of electrons above and below its π bond, an alkene is a **nucleophile.**
- Nucleophiles are attracted to electron-deficient species, called **electrophiles.**
- Alkenes undergo **electrophilic addition reactions.**
- The **mechanism of a reaction** describes the step-by-step process by which reactants are changed into products.
- **Curved arrows** show the bonds that are formed and the bonds that are broken in a reaction.
- A **reaction coordinate diagram** shows the energy changes that take place during the course of a reaction.
- **Thermodynamics** describes a reaction at equilibrium; **kinetics** describes how fast the reaction occurs.
- The more stable a species, the lower its energy.
- As reactants are converted into products, a reaction passes through a maximum-energy **transition state.**
- An **intermediate** is a product of one step of a reaction and a reactant of the next step.
- Transition states have partially formed bonds; intermediates have fully formed bonds.
- The **rate-determining step** has its transition state at the highest point on the reaction coordinate.
- The equilibrium constant, K_{eq}, gives the relative concentrations of reactants and products at equilibrium.
- The more stable the product relative to the reactant, the greater is its concentration at equilibrium and the greater the K_{eq}.
- **Le Châtelier's principle** states that if an equilibrium is disturbed, the system will adjust in a direction to offset the disturbance.
- If the products are more stable than reactants, then K_{eq} is > 1, $\Delta G°$ is negative, and the reaction is **exergonic.**
- If the reactants are more stable than products, then K_{eq} is < 1, $\Delta G°$ is positive, and the reaction is **endergonic.**
- $\Delta G°$ is the **Gibbs free-energy change,** with $\Delta G° = \Delta H° - T\Delta S°$.
- $\Delta H°$ is the change in **enthalpy,** which is the heat given off or consumed as a result of bond making and bond breaking.
- $\Delta S°$ is the change in **entropy,** which is the change in the freedom of motion of the system.
- The formation of products with stronger bonds and greater freedom of motion causes $\Delta G°$ to be negative.
- $\Delta G°$ and K_{eq} are related by the formula $\Delta G° = -RT \ln K_{eq}$.
- **Catalytic hydrogenation** reduces alkenes to alkanes.
- The **heat of hydrogenation** is the heat released in a hydrogenation reaction. It is the $\Delta H°$ value without the negative sign.
- The **most stable alkene** has the **smallest heat of hydrogenation.**
- The stability of an alkene increases as the number of alkyl substituents bonded to its sp^2 carbons increases.
- **Trans alkenes** are more stable than **cis alkenes** because of steric strain.
- The free energy of activation, $\Delta G^{\ddagger}$, is the energy barrier of a reaction. It is the difference between the free energy of the reactants and the free energy of the transition state.
- The rate of the reaction increases as $\Delta G^{\ddagger}$ decreases.
- Anything that makes the reactant more stable or makes the transition state less stable increases the rate constant for the reaction.
- **Kinetic stability** is given by $\Delta G^{\ddagger}$; **thermodynamic stability** is given by $\Delta G°$.
- The **rate** of a reaction depends on the concentration of the reactants, the temperature, and the rate constant.
- A **catalyst** decreases the energy barrier that has to be overcome in the process of converting the reactants into products.
- A catalyst is neither consumed nor changed during the reaction.
- A catalyst does not change the *amount* of product formed, it changes only the *rate* at which the product is formed.
- Most biological catalysts are proteins called **enzymes.**
- **Molecular recognition** is the ability of one molecule to recognize another molecule.

PROBLEMS

21. What is each compound's systematic name?

a.

b. H_3C, CH_3

c. Cl

22. Draw the structure of a hydrocarbon that has six carbon atoms and
- **a.** three vinylic hydrogens and two allylic hydrogens.
- **b.** three vinylic hydrogens and one allylic hydrogen.
- **c.** three vinylic hydrogens and no allylic hydrogens.

23. Which of the following compounds is the most stable? Which is the least stable?

3,4-dimethyl-2-hexene; 2,3-dimethyl-2-hexene; 4,5-dimethyl-2-hexene

24. Draw the condensed structure for each of the following:
- **a.** (*Z*)-1,3,5-tribromo-2-pentene
- **b.** (*Z*)-3-methyl-2-heptene
- **c.** (*E*)-1,2-dibromo-3-isopropyl-2-hexene
- **d.** vinyl bromide
- **e.** 1,2-dimethylcyclopentene
- **f.** diallylamine

25. Draw the skeletal structures for the compounds in Problem 24.

26. **a.** Draw the condensed structures and give the systematic names for all the alkenes with molecular formula C_6H_{12}, ignoring stereoisomers. (*Hint:* There are 13.)
- **b.** Which of the alkenes have *E* and *Z* isomers?
- **c.** Which of the alkenes is the most stable?

27. Draw curved arrows to show the flow of electrons responsible for the conversion of the reactants into the products:

N:, Cl ⟶ N^+ + Cl^-

28. Name the following:

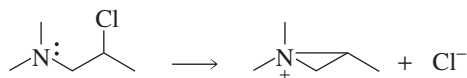
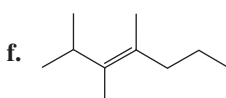
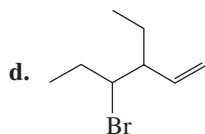
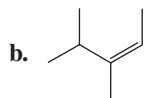
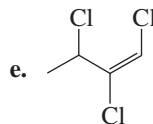
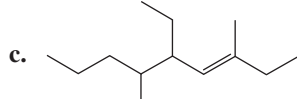
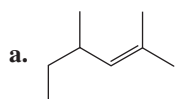
a.

b.

c.

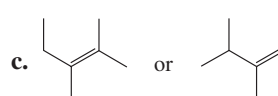
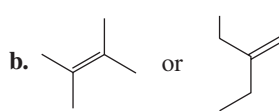
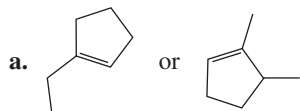
d. Br

e. Cl, Cl, Cl

f.

29. Which is more stable?

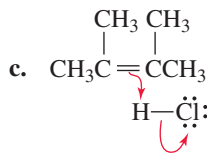
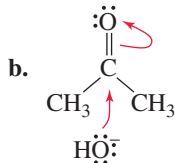
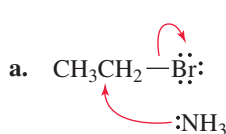
a. or

b. or

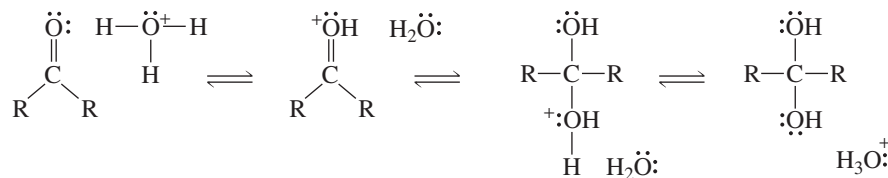
c. or

30. By following the curved red arrows, draw the product(s) of each of the following reaction steps. For each reaction, indicate which reactant is the electrophile and which is the nucleophile.

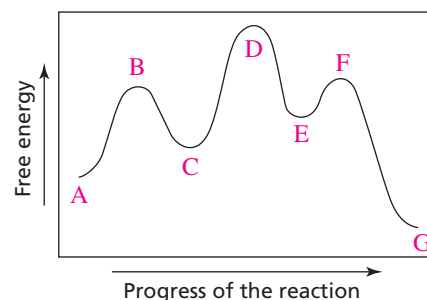
a. CH_3CH_2—Br: , :NH_3

b. :O:, C, CH_3, CH_3, HO^-

c. $CH_3C{=}CCH_3$ (CH_3, CH_3), H—Cl:

31. How many of the following names are correct? Correct the incorrect names.
- **a.** 3,4-dimethylpentane
- **b.** 3,6,8-trimethyldecane
- **c.** 4-ethyl-6-methyloctane
- **d.** 2,8-dimethyl-4-ethylnonane
- **e.** 3-methyl-6-ethyloctane
- **f.** 3-methyl-5-ethyloctane
- **g.** (3Z,6Z)-3,6-dimethyl-3,6-decadiene
- **h.** 2-chloro-1-pentene
- **i.** 3,3,4-trimethyl-1-decene

32. Draw a reaction coordinate diagram for a two-step reaction in which the products of the first step are less stable than the reactants, the reactants of the second step are less stable than the products of the second step, the final products are less stable than the initial reactants, and the second step is the rate-determining step. Label the reactants, products, intermediates, and transition states.

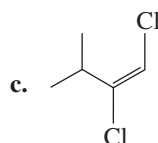
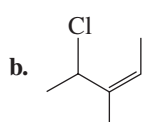
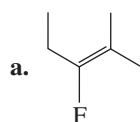
33. Using curved arrows, show the mechanism of the following reaction:

34. a. How many alkenes could you treat with H_2, Pd/C in order to prepare methylcyclopentane?
b. Which of the alkenes is the most stable?
c. Which of the alkenes has the smallest heat of hydrogenation?

35. Given the reaction coordinate diagram for the reaction of **A** to form **G,** answer the following questions:
a. How many intermediates are formed in the reaction?
b. Which letters represent transition states?
c. What is the fastest step in the reaction?
d. Which is more stable, A or G?
e. Does A or E form faster from C?
f. What is the reactant of the rate-determining step?
g. Is the first step of the reaction exergonic or endergonic?
h. Is the overall reaction exergonic or endergonic?
i. Which is the more stable intermediate?
j. Which step in the forward direction has the largest rate constant?
k. Which step in the reverse direction has the smallest rate constant?

36. a. Draw a reaction coordinate diagram for a reaction that is very slow and slightly exergonic.
b. Draw a reaction coordinate diagram for a reaction that is very fast and slightly endergonic.
c. Draw a reaction coordinate diagram for a reaction that is very slow and slightly endergonic.
d. Draw a reaction coordinate diagram for a reaction that is very fast and very exergonic.

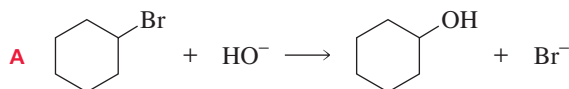
37. Name each of the following:

a.

b. Cl

c. Cl Cl

38. a. Which of the following reactions will have the larger $\Delta S°$ value?
b. Will the $\Delta S°$ value be positive or negative?

A Br + HO^- ⟶ OH + Br^-

B

39. Given that the twist-boat conformer of cyclohexane is 5.3 kcal/mol higher in free energy than the chair conformer, calculate the percentage of twist-boat conformers present in a sample of cyclohexane at 25 °C. Does your answer agree with the statement made on page 131 about the relative number of molecules in these two conformations?

40. a. The $\Delta G°$ for conversion of "axial" fluorocyclohexane to "equatorial" fluorocyclohexane at 25 °C is −0.25 kcal/mol. Calculate the percentage of fluorocyclohexane molecules that have the fluoro substituent in an equatorial position at equilibrium.
b. Do the same calculation for isopropylcyclohexane (its $\Delta G°$ value at 25 °C is −2.1 kcal/mol).
c. Why is the percentage of molecules with the substituent in an equatorial position greater for isopropylcyclohexane?

TUTORIAL

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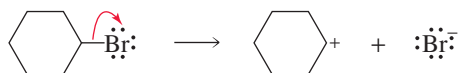
AN EXERCISE IN DRAWING CURVED ARROWS: PUSHING ELECTRONS

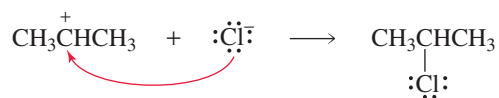
This is an extension of what you learned about drawing curved arrows on pages 179–180. Working through these problems will take only a little of your time. It will be time well spent, however, because curved arrows are used throughout the text and it is important that you are comfortable with this notation. (You will not encounter some of the reaction steps shown in this exercise for weeks or even months to come yet, so don't worry about why the chemical changes take place.)

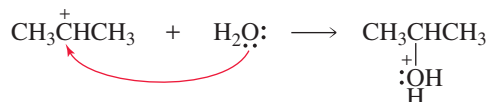
Chemists use curved arrows to show how electrons move as covalent bonds break and/or new covalent bonds form. The tail of the arrow is positioned at the point where the electrons are in the reactant, and the head of the arrow points to where these same electrons end up in the product.

In the following reaction step, the bond between bromine and a carbon of the cyclohexane ring breaks and both electrons in the bond end up with bromine in the product. Thus, **the arrow starts at the electrons that carbon and bromine share in the reactant,** and **the head of the arrow points at bromine** because this is where the two electrons end up in the product.

$$\text{C}_6\text{H}_{11}\text{—}\ddot{\text{Br}}\text{:} \longrightarrow \text{C}_6\text{H}_{11}^{+} + \text{:}\ddot{\text{Br}}\text{:}^{-}$$

Notice that the carbon of the cyclohexane ring is positively charged in the product. This is because it has lost the two electrons it was sharing with bromine. The bromine is negatively charged in the product because it has gained the electrons that it shared with carbon in the reactant. The fact that two electrons move in this example is indicated by the two barbs on the arrowhead.

Notice that the arrow *always* starts at a bond or at a lone pair. It does *not* start at a negative charge. (And since an arrow starts at a pair of electrons, it would never start at a positive charge!)

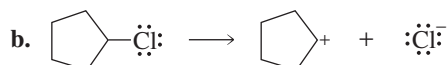
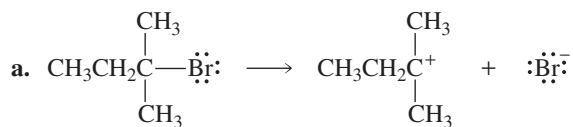
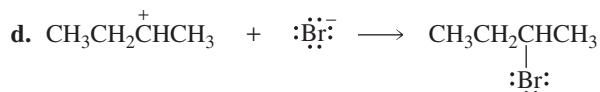
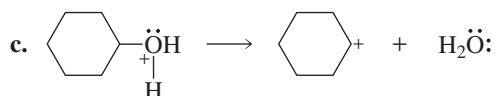
$$CH_3\overset{+}{C}HCH_3 + \text{:}\ddot{\text{Cl}}\text{:}^{-} \longrightarrow CH_3\underset{\text{:}\ddot{\text{Cl}}\text{:}}{\underset{|}{C}}HCH_3$$

In the following reaction step, a bond is being formed between the oxygen of water and a carbon of the other reactant. The arrow starts at one of the lone pairs of the oxygen and points at the atom (the carbon) that will share the electrons in the product. The oxygen in the product is positively charged, because the electrons that oxygen had to itself in the reactant are now being shared with carbon. The carbon that was positively charged in the reactant is not charged in the product, because it has gained a share in a pair of electrons.

$$CH_3\overset{+}{C}HCH_3 + H_2\ddot{O}\text{:} \longrightarrow CH_3\underset{\text{:}\overset{+}{O}H_2}{\underset{|}{C}}HCH_3$$

PROBLEM 1 Draw curved arrows to show the movement of the electrons in the following reaction steps. (The answers to all problems appear immediately after Problem 10.)

a. $CH_3CH_2C(CH_3)_2\text{—}\ddot{\text{Br}}\text{:} \longrightarrow CH_3CH_2\overset{+}{C}(CH_3)_2 + \text{:}\ddot{\text{Br}}\text{:}^{-}$

b. $\text{C}_5\text{H}_9\text{—}\ddot{\text{Cl}}\text{:} \longrightarrow \text{C}_5\text{H}_9^{+} + \text{:}\ddot{\text{Cl}}\text{:}^{-}$

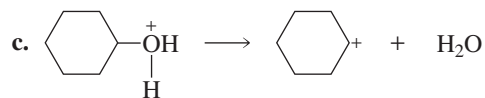
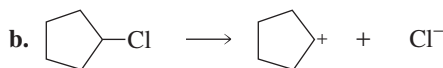
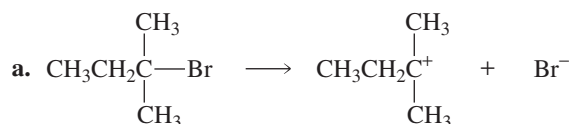
c. Cyclohexyl–$\ddot{O}H$ (with $\overset{+}{}$ and H) ⟶ cyclohexyl cation$^+$ + $H_2\ddot{O}$:

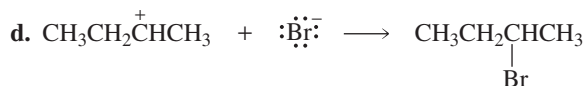
d. $CH_3CH_2\overset{+}{C}HCH_3$ + $:\ddot{Br}:^-$ ⟶ $CH_3CH_2CHCH_3$ with $:\ddot{Br}:$ attached

Frequently, chemists do not show the lone-pair electrons when they write reactions. Problem 2 shows the same reaction steps you just saw in Problem 1, except that the lone pairs are not shown.

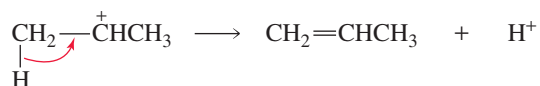
PROBLEM 2 Draw curved arrows to show the movement of the electrons in the following reaction steps:

a. $CH_3CH_2C(CH_3)_2$—Br ⟶ $CH_3CH_2\overset{+}{C}(CH_3)_2$ + Br^-

b. Cyclopentyl—Cl ⟶ cyclopentyl cation$^+$ + Cl^-

c. Cyclohexyl—$\overset{+}{O}H$ (with H) ⟶ cyclohexyl cation$^+$ + H_2O

The lone-pair electrons on Br^- in part **d** have to be shown in the reactant, because an arrow can start only at a bond or at a lone pair. The lone-pair electrons on Br in the product do not have to be shown. It is never wrong to shown lone pairs, but the only time they have to be shown is when an arrow is going to start from the lone pair.

d. $CH_3CH_2\overset{+}{C}HCH_3$ + $:\ddot{Br}:^-$ ⟶ $CH_3CH_2CHCH_3$ with Br attached

Many reaction steps involve both bond breaking and bond formation. In the following example, one bond breaks and one bond forms; the electrons in the bond that breaks are the same as the electrons in the bond that forms. Accordingly, only one arrow is needed to show how the electrons move. As in the previous examples, the arrow starts at the point where the electrons are in the reactant, and the head of the arrow points to where these same electrons end up in the product. Notice that the atom that loses a share in a pair of electrons ends up with a positive charge.

$CH_2(H)$—$\overset{+}{C}HCH_3$ ⟶ $CH_2{=}CHCH_3$ + H^+

Frequently, the electrons in the bond that breaks are not the same as the electrons in the bond that forms. In such cases, two arrows are needed to show the movement of the electrons—one to show the bond that forms and one to show the bond that breaks. In each of the following examples, look at the arrows that illustrate how the electrons move. Notice how the movement of the electrons allows you to determine both the structure of the products and the charges on the products.

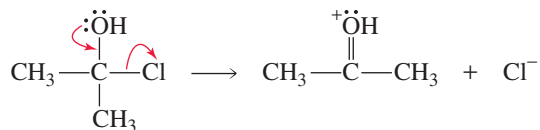
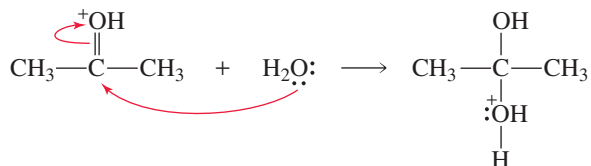
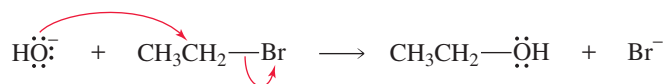
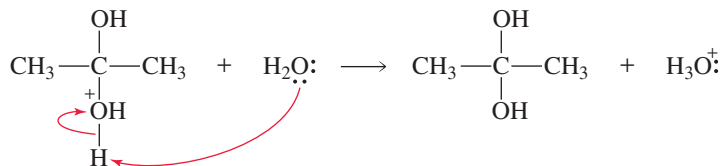
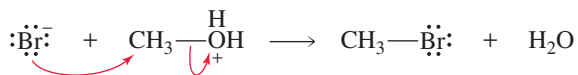
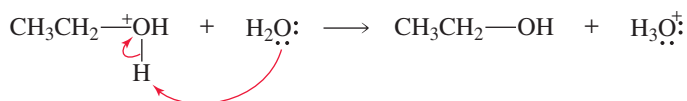
CH_3—C($:\ddot{O}H$)(CH_3)—Cl ⟶ CH_3—C(=$\overset{+}{\ddot{O}}H$)—CH_3 + Cl^-

$$CH_3CH_2—\overset{+}{O}H(—H) + H_2\ddot{O}: \longrightarrow CH_3CH_2—OH + H_3\overset{+}{O}:$$

$$:\ddot{Br}:^- + CH_3—\overset{+}{O}H(H) \longrightarrow CH_3—\ddot{Br}: + H_2O$$

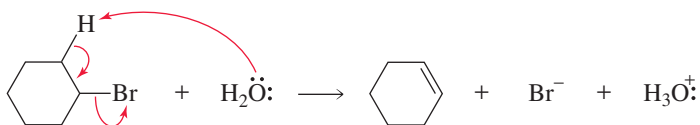
$$CH_3—C(OH)(\overset{+}{O}H—H)—CH_3 + H_2\ddot{O}: \longrightarrow CH_3—C(OH)(OH)—CH_3 + H_3\overset{+}{O}:$$

$$H\ddot{O}:^- + CH_3CH_2—Br \longrightarrow CH_3CH_2—\ddot{O}H + Br^-$$

$$CH_3—C(=\overset{+}{O}H)—CH_3 + H_2\ddot{O}: \longrightarrow CH_3—C(OH)(\overset{+}{:O}H—H)—CH_3$$

In the next reaction, two bonds break and one bond forms; two arrows are needed to show the movement of the electrons.

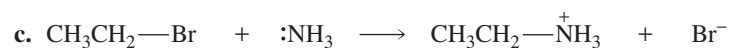
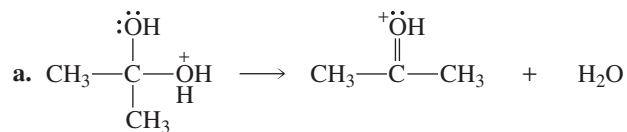
$$CH_3CH{=}CH_2 + H—Br \longrightarrow CH_3\overset{+}{C}HCH_3 + Br^-$$

In the next reaction, two bonds break and two bonds form; three arrows are needed to show the movement of the electrons.

$$\text{(cyclohexane with H and Br)} + H_2\ddot{O}: \longrightarrow \text{cyclohexene} + Br^- + H_3\overset{+}{O}:$$

PROBLEM 3 Draw curved arrows to show the movement of the electrons that result in the formation of the given product(s). (*Hint:* Look at the structure of the product to see what bonds need to be formed and broken in order to arrive at the structure of the desired product.)

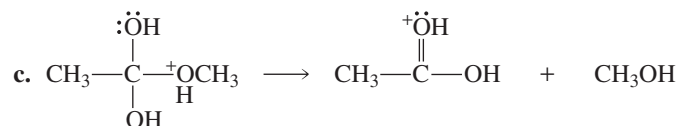
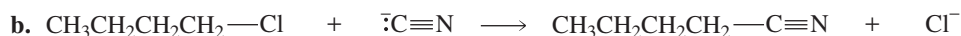
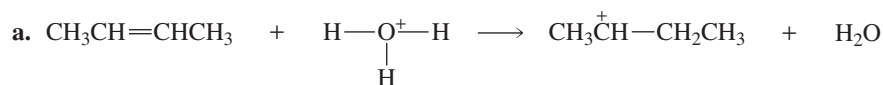
a. $CH_3—C(:\ddot{O}H)(CH_3)—\overset{+}{O}H(H) \longrightarrow CH_3—C(=\overset{+}{\ddot{O}}H)—CH_3 + H_2O$

b. $CH_3CH_2CH{=}CH_2 + H—Cl \longrightarrow CH_3CH_2\overset{+}{C}H—CH_3 + Cl^-$

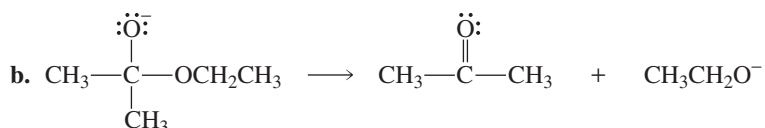
c. $CH_3CH_2—Br + :NH_3 \longrightarrow CH_3CH_2—\overset{+}{N}H_3 + Br^-$

PROBLEM 4 Draw curved arrows to show the movement of the electrons that result in formation of the given product(s).

a. $CH_3CH{=}CHCH_3 + H{-}\overset{+}{O}(H){-}H \longrightarrow CH_3\overset{+}{C}H{-}CH_2CH_3 + H_2O$

b. $CH_3CH_2CH_2CH_2{-}Cl + {}^{-}{:}C{\equiv}N \longrightarrow CH_3CH_2CH_2CH_2{-}C{\equiv}N + Cl^-$

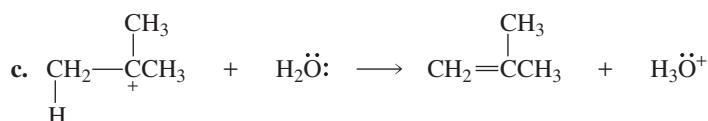
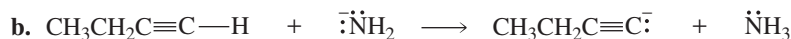
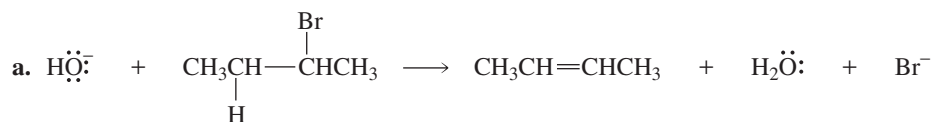
c. $CH_3{-}C(\ddot{O}H)(OH){-}\overset{+}{O}(H)CH_3 \longrightarrow CH_3{-}C({=}\overset{+}{\ddot{O}}H){-}OH + CH_3OH$

PROBLEM 5 Draw curved arrows to show the movement of the electrons that result in formation of the given product(s).

a. $CH_3CH_2CH_2{-}Br + CH_3\ddot{O}{:}^- \longrightarrow CH_3CH_2CH_2{-}\ddot{O}CH_3 + Br^-$

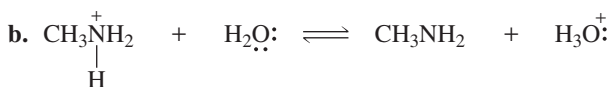
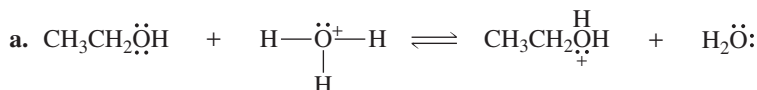
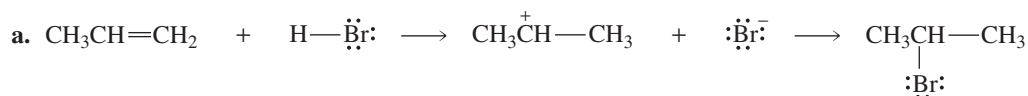
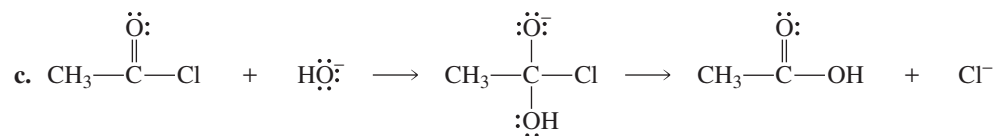
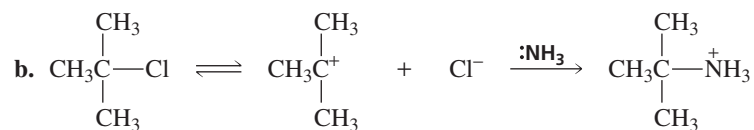
b. $CH_3{-}C(\ddot{O}{:}^-)(CH_3){-}OCH_2CH_3 \longrightarrow CH_3{-}C({=}\ddot{O}{:}){-}CH_3 + CH_3CH_2O^-$

PROBLEM 6 Draw curved arrows to show the movement of the electrons that result in formation of the given product(s).

a. $H\ddot{O}{:}^- + CH_3CH(H){-}CH(Br)CH_3 \longrightarrow CH_3CH{=}CHCH_3 + H_2\ddot{O}{:} + Br^-$

b. $CH_3CH_2C{\equiv}C{-}H + {}^{-}{:}\ddot{N}H_2 \longrightarrow CH_3CH_2C{\equiv}C{:}^- + \ddot{N}H_3$

c. $CH_2(H){-}\overset{+}{C}(CH_3)CH_3 + H_2\ddot{O}{:} \longrightarrow CH_2{=}C(CH_3)CH_3 + H_3\ddot{O}^+$

PROBLEM 7 Draw curved arrows to show the movement of the electrons that result in formation of the given product(s).

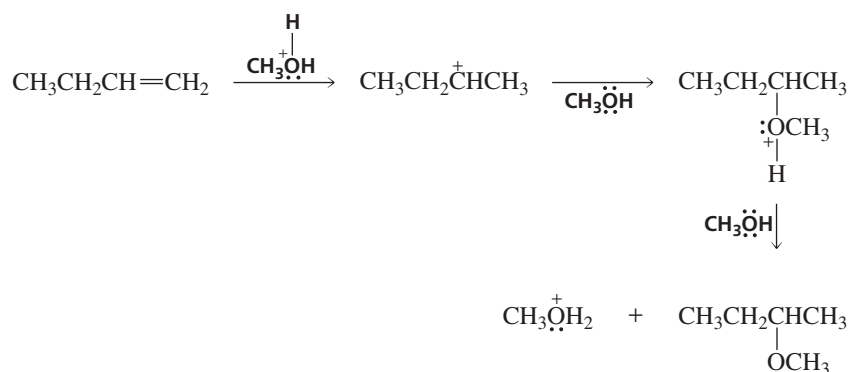
a. $CH_3CH_2\ddot{O}H + H{-}\overset{+}{\ddot{O}}(H){-}H \rightleftharpoons CH_3CH_2\overset{+}{\ddot{O}}H(H) + H_2\ddot{O}{:}$

b. $CH_3\overset{+}{N}H_2(H) + H_2\ddot{O}{:} \rightleftharpoons CH_3NH_2 + H_3\overset{+}{\ddot{O}}$

PROBLEM 8 Draw curved arrows to show the movement of the electrons in each step of the following reaction sequences. (*Hint:* You can tell how to draw the arrows for each step by looking at the products that are formed in that step as a result of the movement of electrons.)

a. $CH_3CH{=}CH_2 + H{-}\ddot{Br}{:} \longrightarrow CH_3\overset{+}{C}H{-}CH_3 + {:}\ddot{Br}{:}^- \longrightarrow CH_3CH({:}\ddot{Br}{:}){-}CH_3$

b. $CH_3C(CH_3)_2-Cl \rightleftharpoons CH_3C^+(CH_3)_2 + Cl^- \xrightarrow{:NH_3} CH_3C(CH_3)_2-\overset{+}{N}H_3$

c. $CH_3-C(=\ddot{O}:)-Cl + H\ddot{O}:^- \longrightarrow CH_3-C(:\ddot{O}:^-)(:\ddot{O}H)-Cl \longrightarrow CH_3-C(=\ddot{O}:)-OH + Cl^-$

PROBLEM 9 Draw curved arrows to show the movement of the electrons in each step of the following reaction sequence:

$$CH_3CH_2CH{=}CH_2 \xrightarrow{CH_3\overset{+}{\ddot{O}}H-H} CH_3CH_2\overset{+}{C}HCH_3 \xrightarrow{CH_3\ddot{O}H} CH_3CH_2CH(:\overset{+}{O}(H)CH_3)CH_3 \xrightarrow{CH_3\ddot{O}H} CH_3\overset{+}{\ddot{O}}H_2 + CH_3CH_2CH(OCH_3)CH_3$$

PROBLEM 10 Use what the curved arrows tell you about electron movement to determine the product of each reaction step.

a. $CH_3CH_2\ddot{O}:^- + CH_3-Br \longrightarrow$

b. $CH_3-C(=\overset{+}{\ddot{O}}H)-OCH_3 + H_2\ddot{O}: \longrightarrow$

c. $H\ddot{O}:^- + CH_3CH_2CH(H)-CH_2-Br \longrightarrow$

d. $CH_3CH_2-C(:\ddot{O}:^-)(OH)-NH_2 \longrightarrow$

e. $CH_3-C(CH_3)_2-\overset{+}{O}H(H) \longrightarrow$

f. $CH_3-C(:\ddot{O}H)(OH)-\overset{+}{O}CH_3(H) \longrightarrow$

ANSWERS TO PROBLEMS ON DRAWING CURVED ARROWS

PROBLEM 1 Answer

a. $CH_3CH_2C(CH_3)_2{-}\ddot{\underset{..}{Br}}\!:\ \longrightarrow\ CH_3CH_2C^+(CH_3)_2\ +\ :\ddot{\underset{..}{Br}}\!:^-$

b. Cyclopentyl$-\ddot{\underset{..}{Cl}}\!:\ \longrightarrow$ cyclopentyl cation $(^+)\ +\ :\ddot{\underset{..}{Cl}}\!:^-$

c. Cyclohexyl$-\overset{+}{\ddot{O}}H(H)\ \longrightarrow$ cyclohexyl cation $(^+)\ +\ H_2\ddot{O}\!:$

d. $CH_3CH_2\overset{+}{C}HCH_3\ +\ :\ddot{\underset{..}{Br}}\!:^-\ \longrightarrow\ CH_3CH_2CH(\!:\ddot{\underset{..}{Br}}\!:)CH_3$

PROBLEM 2 Answer

a. $CH_3CH_2C(CH_3)_2{-}Br\ \longrightarrow\ CH_3CH_2C^+(CH_3)_2\ +\ Br^-$

b. Cyclopentyl$-Cl\ \longrightarrow$ cyclopentyl cation $(^+)\ +\ Cl^-$

c. Cyclohexyl$-\overset{+}{O}H(H)\ \longrightarrow$ cyclohexyl cation $(^+)\ +\ H_2O$

d. $CH_3CH_2\overset{+}{C}HCH_3\ +\ :\ddot{\underset{..}{Br}}\!:^-\ \longrightarrow\ CH_3CH_2CH(Br)CH_3$

PROBLEM 3 Answer

a. $CH_3{-}C(:\ddot{O}H)(CH_3){-}\overset{+}{O}H(H)\ \longrightarrow\ CH_3{-}C(={}^+\ddot{O}H){-}CH_3\ +\ H_2O$

b. $CH_3CH_2CH{=}CH_2\ +\ H{-}Cl\ \longrightarrow\ CH_3CH_2\overset{+}{C}H{-}CH_3\ +\ Cl^-$

c. $CH_3CH_2{-}Br\ +\ :NH_3\ \longrightarrow\ CH_3CH_2{-}\overset{+}{N}H_3\ +\ Br^-$

PROBLEM 4 Answer

a. $CH_3CH{=}CHCH_3 + H{-}\overset{+}{O}(H){-}H \longrightarrow CH_3\overset{+}{C}H{-}CH_2CH_3 + H_2O$

b. $CH_3CH_2CH_2CH_2{-}Cl + {}^{-}:C{\equiv}N \longrightarrow CH_3CH_2CH_2CH_2{-}C{\equiv}N + Cl^{-}$

c. $CH_3{-}C(:\ddot{O}H)(OH){-}\overset{+}{\ddot{O}}(H)CH_3 \longrightarrow CH_3{-}C(={}^{+}\ddot{O}H){-}OH + CH_3OH$

PROBLEM 5 Answer

a. $CH_3CH_2CH_2{-}Br + CH_3\ddot{O}:^{-} \longrightarrow CH_3CH_2CH_2{-}\ddot{O}CH_3 + Br^{-}$

b. $CH_3{-}C(:\ddot{O}:^{-})(CH_3){-}OCH_2CH_3 \longrightarrow CH_3{-}C(=\ddot{O}:){-}CH_3 + CH_3CH_2O^{-}$

PROBLEM 6 Answer

a. $H\ddot{O}:^{-} + CH_3CH(H){-}CH(Br)CH_3 \longrightarrow CH_3CH{=}CHCH_3 + H_2\ddot{O}: + Br^{-}$

b. $CH_3CH_2C{\equiv}C{-}H + {}^{-}:NH_2 \longrightarrow CH_3CH_2C{\equiv}C:^{-} + :NH_3$

c. $CH_2(H){-}\overset{+}{C}(CH_3)CH_3 + H_2\ddot{O}: \longrightarrow CH_2{=}C(CH_3)CH_3 + H_3\ddot{O}^{+}$

PROBLEM 7 Answer

a. $CH_3CH_2\ddot{O}H + H{-}\overset{+}{\ddot{O}}(H){-}H \rightleftharpoons CH_3CH_2\overset{+}{\ddot{O}}(H)H + H_2\ddot{O}:$

b. $CH_3\overset{+}{N}H_2(H) + H_2\ddot{O}: \rightleftharpoons CH_3NH_2 + H_3\overset{+}{O}:$

PROBLEM 8 Answer

a. $CH_3CH{=}CH_2 + H{-}:\ddot{Br}: \longrightarrow CH_3\overset{+}{C}H{-}CH_3 + :\ddot{Br}:^{-} \longrightarrow CH_3CH(:\ddot{Br}:){-}CH_3$

b. $(CH_3)_3C{-}Cl \rightleftharpoons (CH_3)_3C^+ + Cl^- \xrightarrow{:NH_3} (CH_3)_3C{-}\overset{+}{N}H_3$

c. $CH_3{-}C({=}O){-}Cl + HO^- \longrightarrow CH_3{-}C(O^-)(OH){-}Cl \longrightarrow CH_3{-}C({=}O){-}OH + Cl^-$

PROBLEM 9 Answer

$CH_3CH_2CH{=}CH_2 \xrightarrow{CH_3\overset{+}{O}H_2} CH_3CH_2\overset{+}{C}HCH_3 \xrightarrow{CH_3\ddot{O}H} CH_3CH_2CH(\overset{+}{O}(H)CH_3)CH_3 \xrightarrow{CH_3\ddot{O}H} CH_3\overset{+}{O}H_2 + CH_3CH_2CH(OCH_3)CH_3$

PROBLEM 10 Answer

a. $CH_3CH_2O^- + CH_3{-}Br \longrightarrow CH_3CH_2OCH_3 + Br^-$

b. $CH_3{-}C({=}\overset{+}{O}H){-}OCH_3 + H_2O: \longrightarrow CH_3{-}C(OH)(\overset{+}{O}H_2){-}OCH_3$

c. $HO^- + CH_3CH_2CH(H){-}CH_2{-}Br \longrightarrow CH_3CH_2CH{=}CH_2 + H_2O + Br^-$

d. $CH_3CH_2{-}C(O^-)(OH){-}NH_2 \longrightarrow CH_3CH_2{-}C({=}O){-}NH_2 + HO^-$

e. $(CH_3)_3C{-}\overset{+}{O}H_2 \longrightarrow (CH_3)_3C^+ + H_2O$

f. $CH_3{-}C(OH)_2{-}\overset{+}{O}(H)CH_3 \longrightarrow CH_3{-}C({=}\overset{+}{O}H){-}OH + CH_3OH$

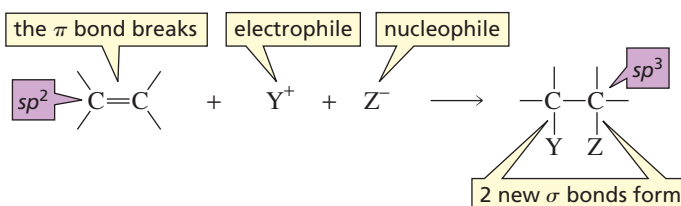
6 The Reactions of Alkenes and Alkynes

Currently, in order to protect our environment, the challenge facing organic chemists is to design syntheses that use reactants and generate products that cause little or no toxicity to the environment. Preventing pollution at the molecular level is known as green chemistry *(see page 211).*

We have seen that organic compounds can be divided into families and that all the members of a family react in the same way (Section 5.2). One family consists of compounds with carbon–carbon double bonds—compounds known as **alkenes.** Another family consists of compounds with carbon–carbon triple bonds—compounds known as **alkynes.** In this chapter, we will first look at the reactions of alkenes and then we will examine the reactions of alkynes.

As you study the reactions of alkenes, look for the feature that they all have in common: *the relatively loosely held π electrons of the carbon–carbon double bond are attracted to an electrophile. Thus, each reaction starts with the addition of an electrophile to one of the* sp^2 *carbons of the alkene and concludes with the addition of a nucleophile to the other* sp^2 *carbon.*

$$\mathrm{C{=}C} + \mathrm{Y^+} + \mathrm{Z^-} \longrightarrow -\underset{\mathrm{Y}}{\underset{|}{\mathrm{C}}}-\underset{\mathrm{Z}}{\underset{|}{\mathrm{C}}}-$$

the π bond breaks
electrophile
nucleophile
sp^2
sp^3
2 new σ bonds form

The end result is that the π bond breaks and the electrophile and nucleophile form new σ bonds with the sp^2 carbons. Notice that the sp^2 carbons in the reactant become sp^3 carbons in the product. The particular product obtained depends only on the *electrophile* and the *nucleophile* used in the addition reaction.

When an electrophile and a nucleophile add to a double bond, the *first* species that adds is the electrophile. Therefore, this characteristic reaction of alkenes is called an **electrophilic addition reaction** (Section 5.3).

Later in the chapter, when you look at the reactions of alkynes, you will see that because alkenes and alkynes belong to the same group of families (Section 5.2), the reactions of alkynes are very similar to those of alkenes—that is, alkynes also undergo electrophilic addition reactions.

Green Chemistry: Aiming for Sustainability

Chemical innovations have improved the quality of virtually every aspect of life: food, shelter, medicine, transportation, communication, and the availability of new materials. These improvements, however, have come with a price—namely, the damage that the development and disposal of chemicals has inflicted on the environment.

Chemists now are focused on sustainability, which is defined as "meeting the needs of the current generation without sacrificing the ability to meet the needs of future generations." One way to achieve sustainability is through the use of green chemistry.

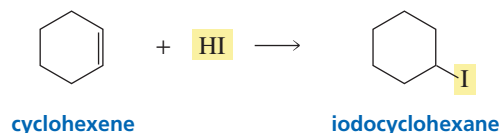
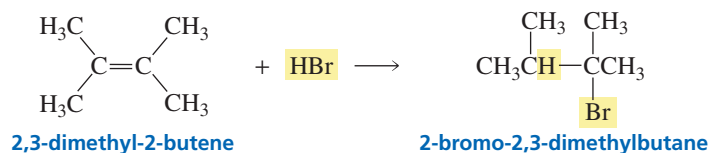
Green chemistry is pollution prevention at the molecular level. It involves the design of chemical products and processes so that the generation of polluting substances is reduced or eliminated. For example, chemists are now creating products not only for function, but also for biodegradability. They are designing syntheses that use and generate substances that cause little or no toxicity to health or to the environment. Green chemical syntheses can be cost effective since they reduce the expense for such things as waste disposal, regulatory compliance, and liability. Applying the principles of green chemistry can help us achieve a sustainable future.

6.1 THE ADDITION OF A HYDROGEN HALIDE TO AN ALKENE

If the reagent that adds to an alkene is a hydrogen halide (HF, HCl, HBr, or HI), the product of the reaction will be an alkyl halide:

$$(CH_3)_2C{=}C(CH_3)_2 + HBr \longrightarrow CH_3CH(CH_3){-}CBr(CH_3)CH_3$$

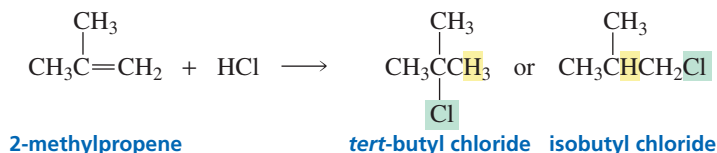
2,3-dimethyl-2-butene → 2-bromo-2,3-dimethylbutane

cyclohexene + HI → iodocyclohexane

Because the electrophile is the *first* species that adds, this characteristic reaction of alkenes is called an electrophilic addition reaction.

Because the alkenes in the preceding reactions have the same substituents on both sp^2 carbons, it is easy to predict the product of the reaction: the electrophile (H^+) adds to either one of the sp^2 carbons and the nucleophile (X^-) adds to the other sp^2 carbon. It does not matter which sp^2 carbon the electrophile adds to because the same product will be obtained in either case.

But what happens if the alkene does *not* have the same substituents on both sp^2 carbons? Which sp^2 carbon gets the hydrogen? For example, does the following reaction form *tert*-butyl chloride or isobutyl chloride?

$$CH_3C(CH_3){=}CH_2 + HCl \longrightarrow CH_3CCl(CH_3)CH_3 \text{ or } CH_3CH(CH_3)CH_2Cl$$

2-methylpropene → *tert*-butyl chloride or isobutyl chloride

To answer this question, we need to carry out this reaction, isolate the products, and identify them. When we do, we find that the only product is *tert*-butyl chloride. If we can find out why it is the only product, then we can use this knowledge to predict the products of other alkene reactions. To do this, we need to look again at the **mechanism of the reaction** (Section 5.3).

Recall that the first step of the reaction—the addition of H^+ to an sp^2 carbon to form either the *tert*-butyl cation or the isobutyl cation—is the slow rate-determining step (Section 5.9). If there is any difference in the rate of formation of these two carbocations, then the one that is formed faster will be the predominant product of the first step. Moreover, the particular carbocation formed in the first step determines the final product of the reaction. That is, if the *tert*-butyl cation is formed, it will react rapidly with Cl^- to form *tert*-butyl chloride. On the other hand, if the isobutyl cation is formed, it will react rapidly with Cl^- to form isobutyl chloride. Since we know that the only product of the reaction is *tert*-butyl chloride, the *tert*-butyl cation must be formed much faster than the isobutyl cation.

A curved arrow with a two-barbed arrowhead signifies the movement of two electrons. The arrow always points *from* the electron donor *to* the electron acceptor.

The carbocation's positive charge is on the sp^2 carbon that does *not* become attached to the proton.

H⁺ adds to C–1

$CH_3\overset{CH_3}{\underset{+}{C}}CH_3 + :\ddot{Cl}:^-$ → $CH_3\overset{CH_3}{\underset{Cl}{C}}CH_3$

tert-butyl cation

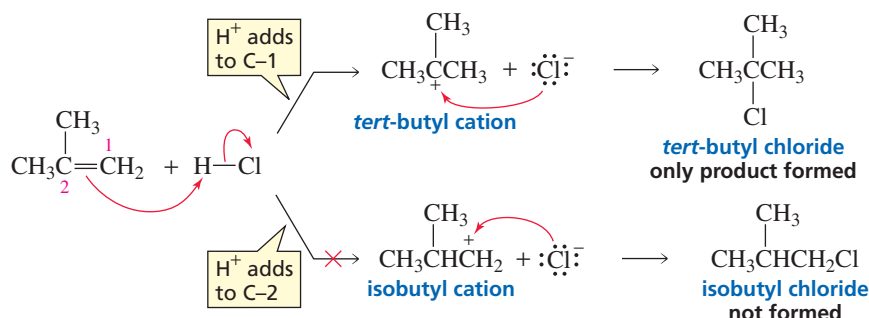
tert-butyl chloride
only product formed

$CH_3\overset{CH_3}{C}{=}CH_2 + H{-}Cl$ (C-2 = CH₃C, C-1 = CH₂)

H⁺ adds to C–2

$CH_3\overset{CH_3}{C}H\overset{+}{C}H_2 + :\ddot{Cl}:^-$ → $CH_3\overset{CH_3}{C}HCH_2Cl$

isobutyl cation

isobutyl chloride
not formed

Why is the *tert*-butyl cation formed faster? To answer this question, we need to look at two things: (1) the factors that affect the stability of a carbocation and (2) how its stability affects the rate at which it is formed.

PROBLEM 1

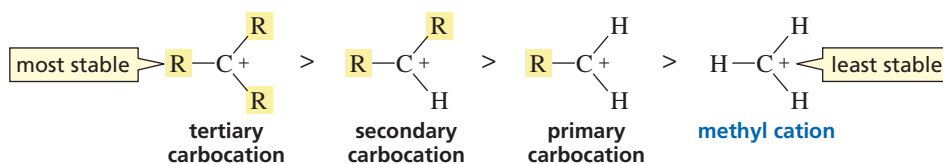
Draw the mechanism for the reaction of cyclohexene with HCl.

6.2 CARBOCATION STABILITY DEPENDS ON THE NUMBER OF ALKYL GROUPS ATTACHED TO THE POSITIVELY CHARGED CARBON

Carbocations are classified based on the carbon that carries the positive charge: a **primary carbocation** has a positive charge on a primary carbon, a **secondary carbocation** has a positive charge on a secondary carbon, and a **tertiary carbocation** has a positive charge on a tertiary carbon.

Tertiary carbocations are more stable than secondary carbocations, and secondary carbocations are more stable than primary carbocations. Thus, we see that the stability of a carbocation increases as the number of alkyl substituents attached to the positively charged carbon increases. These are relative stabilities, however, because carbocations are rarely stable enough to isolate.

relative stabilities of carbocations

most stable → R_3C^+ (tertiary carbocation) > R_2HC^+ (secondary carbocation) > RH_2C^+ (primary carbocation) > H_3C^+ (methyl cation) ← least stable

The more alkyl groups attached to the positively charged carbon, the more stable the carbocation.

Alkyl groups stabilize carbocations because they decrease the concentration of positive charge on the carbon. Notice that the blue area in the following electrostatic potential maps (representing positive charge) is the least intense for the most stable *tert*-butyl cation (a tertiary carbocation) and the most intense for the least stable methyl cation.

Carbocation stability: 3° > 2° > 1°

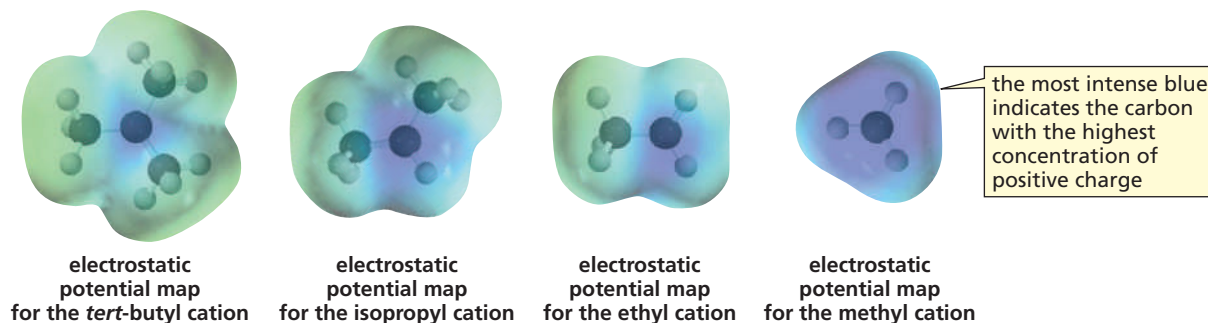
Alkyl substituents stabilize both alkenes and carbocations.

How do alkyl groups decrease the concentration of positive charge on the carbon? Recall that the positive charge on a carbon signifies an empty *p* orbital (Section 1.10). Figure 6.1 shows that in the ethyl cation, the orbital of an adjacent C—H σ bond (the orange orbital) can overlap the empty *p* orbital (the purple orbital). This movement of electrons from a σ bond orbital toward the vacant *p* orbital decreases the charge on the sp^2 carbon and causes a partial positive charge to develop on the two atoms bonded by the overlapping σ bond orbital (the H and the C). With three atoms sharing the positive charge, the carbocation is stabilized because a charged species is more stable if its charge is dispersed over more than one atom (Section 2.8). In contrast, the positive charge in the methyl cation is concentrated solely on one atom.

Figure 6.1
Stabilization of a carbocation by hyperconjugation. In the ethyl cation, the electrons of an adjacent C—H σ bond orbital are delocalized into the empty *p* orbital. Hyperconjugation cannot occur in the methyl cation.

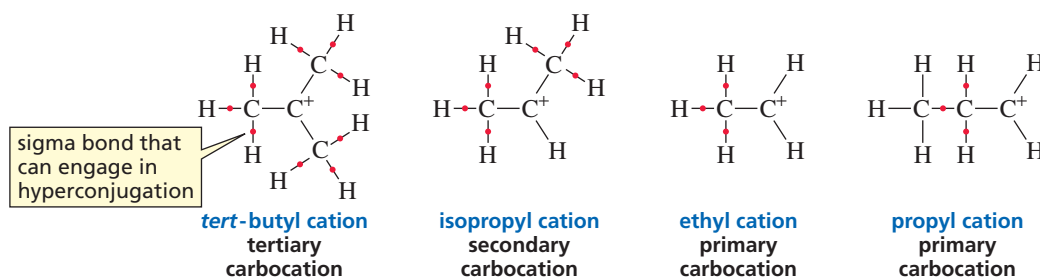
Delocalization of electrons by the overlap of a σ bond orbital with an empty orbital on an adjacent carbon is called **hyperconjugation.** Notice that the σ bond orbitals that can overlap the empty *p* orbital are those *attached to an atom that is attached to the positively charged carbon.* In the *tert*-butyl cation, nine σ bond orbitals can potentially overlap the empty *p* orbital of the positively charged carbon. (The nine σ bonds are indicated by red dots.)

sigma bond that can engage in hyperconjugation

tert-butyl cation
tertiary carbocation

isopropyl cation
secondary carbocation

ethyl cation
primary carbocation

propyl cation
primary carbocation

The isopropyl cation has six such orbitals, whereas the ethyl and propyl cations each have three. Therefore, hyperconjugation stabilizes the tertiary carbocation more than the secondary carbocation, and it stabilizes the secondary carbocation more than either of the primary carbocations. Notice that both C—H and C—C σ bond orbitals can overlap the empty *p* orbital.

PROBLEM 2♦

a. How many σ bond orbitals are available for overlap with the vacant p orbital in the methyl cation?

b. Which is more stable, a methyl cation or an ethyl cation? Why?

PROBLEM 3♦

a. How many σ bond orbitals are available for overlap with the vacant p orbital in

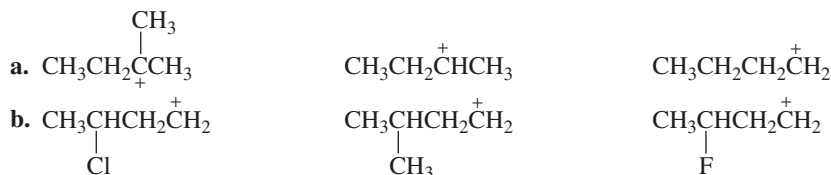
1. the isobutyl cation? **2.** the *n*-butyl cation? **3.** the *sec*-butyl cation?

b. Which of the carbocations in part **a** is most stable?

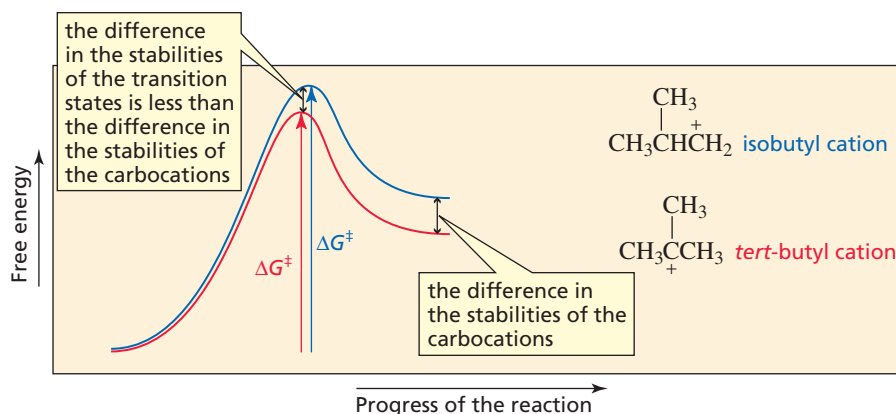
PROBLEM 4♦

List the following carbocations in each set in order from most stable to least stable:

a. $CH_3CH_2\overset{+}{C}(CH_3)CH_3$ $\quad CH_3CH_2\overset{+}{C}HCH_3$ $\quad CH_3CH_2CH_2\overset{+}{C}H_2$

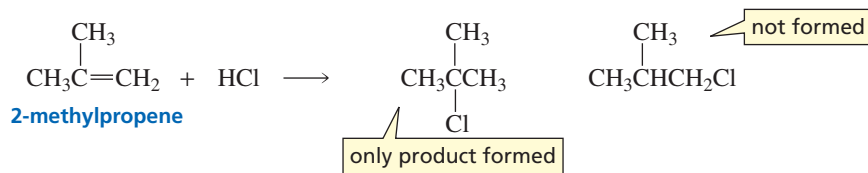
b. $CH_3CH(Cl)CH_2\overset{+}{C}H_2$ $\quad CH_3CH(CH_3)CH_2\overset{+}{C}H_2$ $\quad CH_3CH(F)CH_2\overset{+}{C}H_2$

Now we are prepared to understand why the *tert*-butyl cation is formed faster than the isobutyl cation when 2-methylpropene reacts with HCl. We know that the *tert*-butyl cation (a tertiary carbocation) is more stable than the isobutyl cation (a primary carbocation). The same factors that stabilize the positively charged carbocation also stabilize the transition state for its formation because the transition state has a partial positive charge (Section 5.9). Therefore, the transition state leading to the *tert*-butyl cation is more stable (that is, lower in energy) than the transition state leading to the isobutyl cation (Figure 6.2). (Notice that because the amount of positive charge in the transition state is less than the amount of positive charge in the product, the difference in the stabilities of the two transition states in Figure 6.2 is less than the difference in the stabilities of the two carbocation products.)

The more stable carbocation is formed more rapidly.

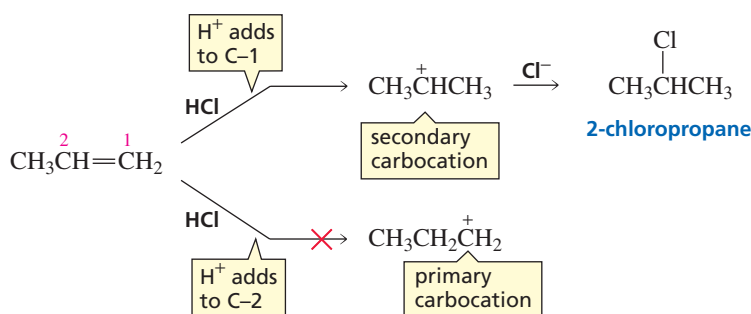
▶ Figure 6.2
Reaction coordinate diagram for the addition of H^+ to 2-methylpropene to form the primary isobutyl cation and the tertiary *tert*-butyl cation.

We have seen that the rate of a reaction is determined by the free energy of activation ($\Delta G^{\ddagger}$), which is the difference between the free energy of the transition state and the free energy of the reactant: the smaller the free energy of activation, the faster the reaction (Section 5.9). Thus, the *tert*-butyl cation will be formed faster than the isobutyl cation. The relative rates of formation of the two carbocations determine the relative amounts of products formed, because formation of the carbocation is the rate-limiting step of the reaction.

If the difference in the rates of formation of the two carbocations is small, both products will be formed, but the major product will be the one formed from reaction of the nucleophile with the faster-formed carbocation. If the difference in the rates is sufficiently large, however, the product formed from reaction of the nucleophile with the

faster-formed carbocation will be the only product; this is what we saw happens when 2-methylpropene reacts with HCl.

$$\underset{\textbf{2-methylpropene}}{CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2} + HCl \longrightarrow \underset{\text{only product formed}}{CH_3\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle Cl}{|}}{C}}}CH_3} \qquad \underset{\text{not formed}}{CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2Cl}$$

6.3 ELECTROPHILIC ADDITION REACTIONS ARE REGIOSELECTIVE

Now that we know that the major product of an electrophilic addition reaction is the one obtained by adding the electrophile to the sp^2 carbon that results in formation of the more stable carbocation, we can predict the major product of the reaction of an unsymmetrical alkene with a hydrogen halide.

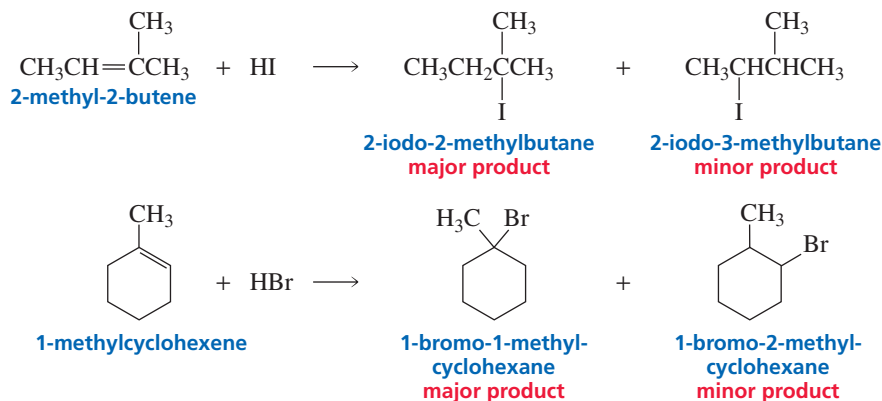
For example, in the following reaction, the proton can add to C-1 to form a secondary carbocation or it can add to C-2 to form a primary carbocation. Because the secondary carbocation is more stable, it is formed more rapidly. (Primary carbocations are so unstable that they form only with great difficulty.) As a result, the only product is 2-chloropropane.

The sp^2 carbon that does not get the proton is the one that is positively charged in the carbocation intermediate.

$$\overset{2}{C}H_3CH{=}\overset{1}{C}H_2 \xrightarrow[\text{H}^+\text{ adds to C–1}]{HCl} \underset{\text{secondary carbocation}}{CH_3\overset{+}{C}HCH_3} \xrightarrow{Cl^-} \underset{\textbf{2-chloropropane}}{CH_3\overset{\displaystyle Cl}{\overset{|}{C}}HCH_3}$$

$$CH_3CH{=}CH_2 \xrightarrow[\text{H}^+\text{ adds to C–2}]{HCl} \not\longrightarrow \underset{\text{primary carbocation}}{CH_3CH_2\overset{+}{C}H_2}$$

Two products are formed in both of the following reactions, but the major product is the one that results from reaction of the nucleophile with the faster formed tertiary carbocation.

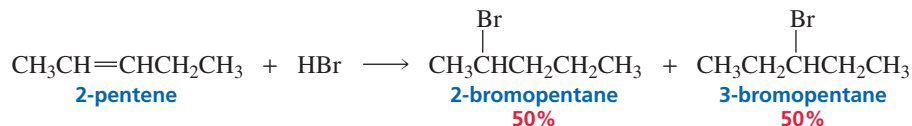
$$\underset{\textbf{2-methyl-2-butene}}{CH_3CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}CH_3} + HI \longrightarrow \underset{\substack{\textbf{2-iodo-2-methylbutane}\\ \text{major product}}}{CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle I}{|}}{C}}}CH_3} + \underset{\substack{\textbf{2-iodo-3-methylbutane}\\ \text{minor product}}}{CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}H\underset{\underset{\displaystyle I}{|}}{C}HCH_3}$$

$$\textbf{1-methylcyclohexene} + HBr \longrightarrow \underset{\substack{\textbf{1-bromo-1-methylcyclohexane}\\ \text{major product}}}{} + \underset{\substack{\textbf{1-bromo-2-methylcyclohexane}\\ \text{minor product}}}{}$$

The two products of each of the preceding reactions are *constitutional isomers.* That is, they have the same molecular formula, but differ in how their atoms are connected. A reaction in which two or more constitutional isomers could be obtained as products, but one of them predominates, is called a **regioselective reaction.**

Regioselectivity is the preferential formation of one constitutional isomer over another.

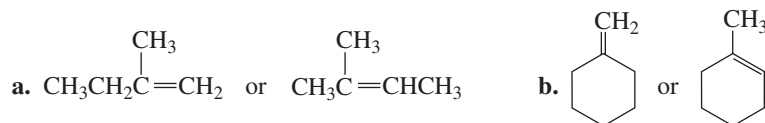
The following reaction is not regioselective. Because the addition of H^+ to either of the sp^2 carbons produces a secondary carbocation, both carbocations are formed at about the same rate. Therefore, approximately equal amounts of the two alkyl halides are obtained.

$$CH_3CH{=}CHCH_2CH_3 + HBr \longrightarrow CH_3CH(Br)CH_2CH_2CH_3 + CH_3CH_2CH(Br)CH_2CH_3$$

2-pentene → 2-bromopentane 50% + 3-bromopentane 50%

PROBLEM 5♦

To which compound is the addition of HBr more highly regioselective?

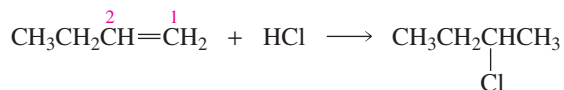
a. $CH_3CH_2C(CH_3){=}CH_2$ or $CH_3C(CH_3){=}CHCH_3$

b. methylenecyclohexane ($=CH_2$) or 1-methylcyclohexene (CH_3)

The electrophile adds preferentially to the sp^2 carbon bonded to the most hydrogens.

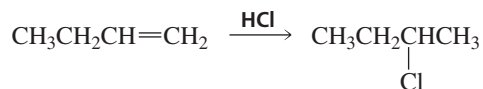
From the reactions we have seen so far, we can devise a rule that applies to all electrophilic additions to alkenes:

> The *electrophile adds preferentially to the* sp^2 *carbon bonded to the most hydrogens* (that is, to the less substituted sp^2 carbon).

The rule is simply a quick way to determine the major product of an electrophilic addition reaction. The answer you get by using the rule will be the same as the answer you get by determining relative carbocation stabilities. In the following reaction, for example,

$$CH_3CH_2\overset{2}{C}H{=}\overset{1}{C}H_2 + HCl \longrightarrow CH_3CH_2CH(Cl)CH_3$$

we can say that the electrophile (in this case, H^+) adds preferentially to C-1 because it is the sp^2 carbon bonded to the most hydrogens. Or we can say that H^+ adds to C-1 to form a secondary carbocation, which is more stable than the primary carbocation that would have to be formed if H^+ added to C-2.

The foregoing examples illustrate the way organic reactions are typically written. The reactants are written to the left of the reaction arrow, and the products are written to the right of the arrow. Any conditions that need to be stipulated, such as the solvent, the temperature, or a catalyst, are written above or below the arrow. Sometimes only the organic (carbon-containing) reagent is written to the left of the arrow, and any other reagents are written above or below the arrow.

$$CH_3CH_2CH{=}CH_2 \xrightarrow{HCl} CH_3CH_2CH(Cl)CH_3$$

PROBLEM 6♦

What would be the major product obtained from the addition of HBr to each of the following compounds?

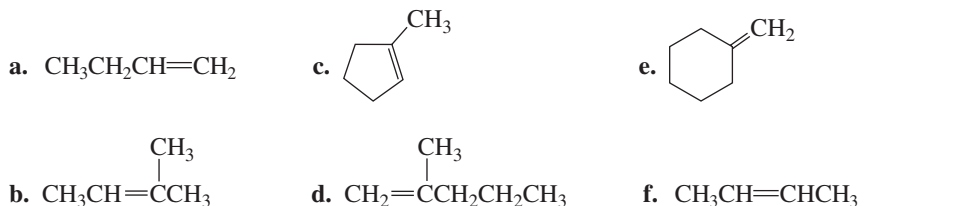
a. $CH_3CH_2CH{=}CH_2$

b. $CH_3CH{=}C(CH_3)CH_3$

c. 1-methylcyclopentene (CH_3)

d. $CH_2{=}C(CH_3)CH_2CH_2CH_3$

e. methylenecyclohexane ($=CH_2$)

f. $CH_3CH{=}CHCH_3$

Which Are More Harmful, Natural Pesticides or Synthetic Pesticides?

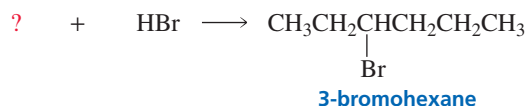
Learning to synthesize new compounds is an important part of organic chemistry. Long before chemists learned to synthesize compounds that would protect plants from predators, plants were doing the job themselves. Plants have every incentive to synthesize pesticides. When you cannot run, you need to find another way to protect yourself. But which pesticides are more harmful, those synthesized by chemists or those synthesized by plants? Unfortunately, we do not know because while federal laws require all human-made pesticides to be tested for any adverse effects, they do not require plant-made pesticides to be tested. Besides, risk evaluations of chemicals are usually done on rats, and something that is harmful to a rat may or may not be harmful to a human. Furthermore, when rats are tested, they are exposed to much higher concentrations of the chemical than would be experienced by a human, and some chemicals are harmful only at high doses. For example, we all need sodium chloride for survival, but high concentrations are poisonous; and, although we associate alfalfa sprouts with healthy eating, monkeys fed very large amounts of alfalfa sprouts have been found to develop an immune system disorder.

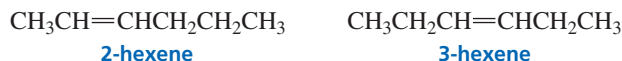
PROBLEM-SOLVING STRATEGY

Planning the Synthesis of an Alkyl Halide

a. What alkene should be used to synthesize 3-bromohexane?

$$? \quad + \quad HBr \longrightarrow CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3$$

3-bromohexane

The best way to answer this kind of question is to begin by listing all the alkenes that could be used. Because you want to synthesize an alkyl halide that has a bromo substituent at the 3-position, the alkene should have an sp^2 carbon at that position. Two alkenes fit the description: 2-hexene and 3-hexene.

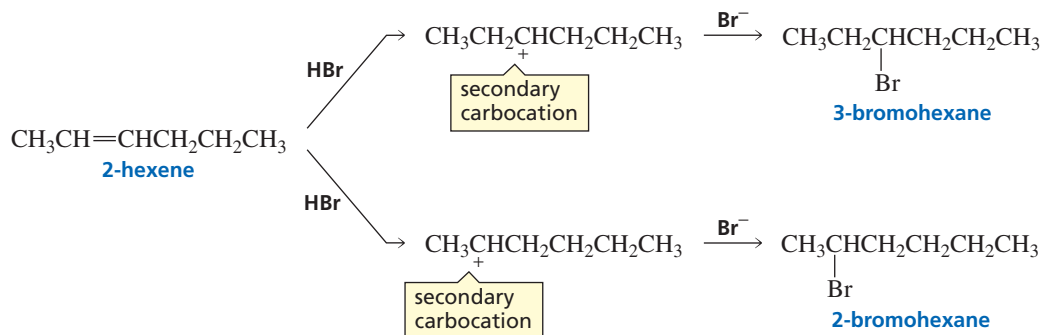
$$CH_3CH{=}CHCH_2CH_2CH_3 \qquad CH_3CH_2CH{=}CHCH_2CH_3$$

2-hexene **3-hexene**

Because there are two possibilities, we next need to decide whether there is any advantage to using one over the other. The addition of H^+ to 2-hexene forms two different secondary carbocations. Because the carbocations have the same stability, approximately equal amounts of each will be formed. Therefore, half the product will be the desired 3-bromohexane and half will be 2-bromohexane.

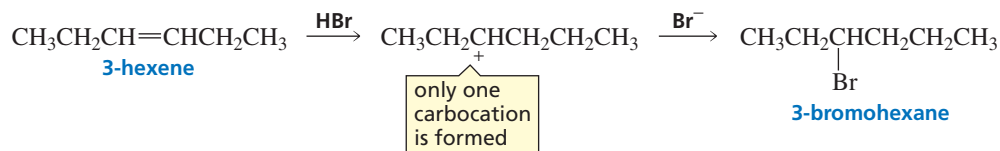
$$CH_3CH{=}CHCH_2CH_2CH_3 \xrightarrow{HBr} CH_3CH_2\overset{+}{C}HCH_2CH_2CH_3 \xrightarrow{Br^-} CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3$$

2-hexene → secondary carbocation → **3-bromohexane**

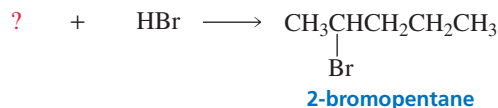
$$CH_3CH{=}CHCH_2CH_2CH_3 \xrightarrow{HBr} CH_3\overset{+}{C}HCH_2CH_2CH_2CH_3 \xrightarrow{Br^-} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_2CH_3$$

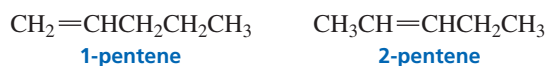
2-hexene → secondary carbocation → **2-bromohexane**

The addition of H^+ to either of the sp^2 carbons of 3-hexene, on the other hand, forms the same carbocation because the alkene is symmetrical. Therefore, all the product (not just half) will be the desired 3-bromohexane. Thus, 3-hexene should be used for the synthesis of the desired compound.

$$CH_3CH_2CH{=}CHCH_2CH_3 \xrightarrow{HBr} CH_3CH_2\overset{+}{C}HCH_2CH_2CH_3 \xrightarrow{Br^-} CH_3CH_2\underset{Br}{C}HCH_2CH_2CH_3$$

3-hexene; only one carbocation is formed; 3-bromohexane

b. What alkene should be used to synthesize 2-bromopentane?

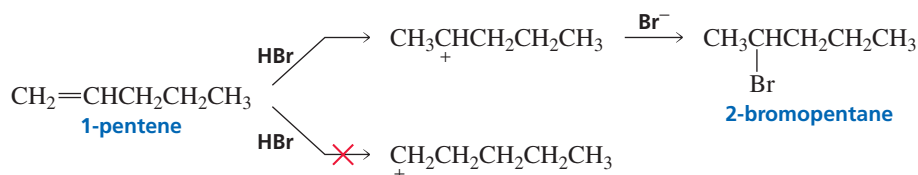
$$? + HBr \longrightarrow CH_3\underset{Br}{C}HCH_2CH_2CH_3$$

2-bromopentane

Either 1-pentene or 2-pentene could be used because both have an sp^2 carbon at the 2-position.

$CH_2{=}CHCH_2CH_2CH_3$ (1-pentene) $\quad CH_3CH{=}CHCH_2CH_3$ (2-pentene)

When H^+ adds to 1-pentene, a secondary and a primary carbocation could be formed. The primary carbocation is so unstable, however, that little, if any, will be formed. Thus, 2-bromopentane will be the only product of the reaction.

$$CH_2{=}CHCH_2CH_2CH_3 \xrightarrow{HBr} CH_3\overset{+}{C}HCH_2CH_2CH_3 \xrightarrow{Br^-} CH_3\underset{Br}{C}HCH_2CH_2CH_3$$

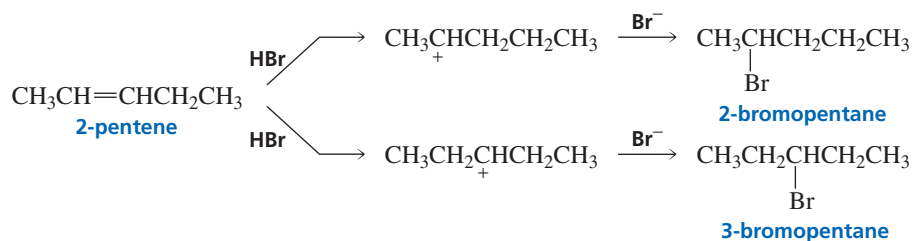
1-pentene → 2-bromopentane

$$CH_2{=}CHCH_2CH_2CH_3 \xrightarrow{HBr} \times\ \overset{+}{C}H_2CH_2CH_2CH_2CH_3$$

When H^+ adds to 2-pentene, on the other hand, two different secondary carbocations can be formed. Because they have the same stability, they will be formed in approximately equal amounts. Thus, only about half of the product will be 2-bromopentane. The other half will be 3-bromopentane.

$$CH_3CH{=}CHCH_2CH_3 \xrightarrow{HBr} CH_3\overset{+}{C}HCH_2CH_2CH_3 \xrightarrow{Br^-} CH_3\underset{Br}{C}HCH_2CH_2CH_3$$

2-pentene → 2-bromopentane

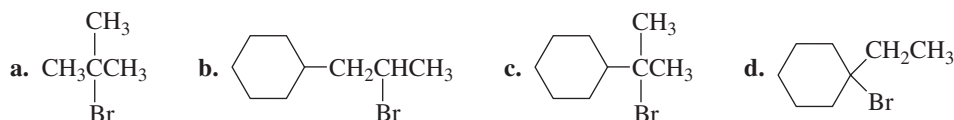
$$CH_3CH{=}CHCH_2CH_3 \xrightarrow{HBr} CH_3CH_2\overset{+}{C}HCH_2CH_3 \xrightarrow{Br^-} CH_3CH_2\underset{Br}{C}HCH_2CH_3$$

2-pentene → 3-bromopentane

Because all the alkyl halide formed from 1-pentene is the desired product, but only half the alkyl halide formed from 2-pentene is the desired product, 1-pentene is the best alkene to use for the synthesis.

Now use the strategy you have just learned to solve Problem 7.

PROBLEM 7♦

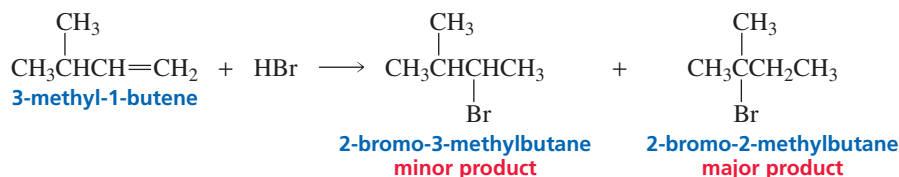
What alkene should be used to synthesize each of the following alkyl bromides?

a. $CH_3C(CH_3)(Br)CH_3$ **b.** cyclohexyl–$CH_2CH(Br)CH_3$ **c.** cyclohexyl–$C(CH_3)(Br)CH_3$ **d.** 1-bromo-1-ethylcyclohexane (ring carbon bearing CH_2CH_3 and Br)

6.4 A CARBOCATION WILL REARRANGE IF IT CAN FORM A MORE STABLE CARBOCATION

Some electrophilic addition reactions give products that are not what you would get by adding an electrophile to the sp^2 carbon bonded to the most hydrogens and a nucleophile to the other sp^2 carbon.

For example, in the following reaction, 2-bromo-3-methylbutane is the product you would get from adding H^+ to the sp^2 carbon bonded to the most hydrogens and adding Br^- to the other sp^2 carbon, but this is a minor product. 2-Bromo-2-methylbutane is an "unexpected" product, and yet it is the major product of the reaction.

$$CH_3CH(CH_3)CH{=}CH_2 + HBr \longrightarrow CH_3CH(CH_3)CHBrCH_3 + CH_3CBr(CH_3)CH_2CH_3$$

3-methyl-1-butene; 2-bromo-3-methylbutane (minor product); 2-bromo-2-methylbutane (major product)

In another example, the following reaction forms both 3-chloro-2,2-dimethylbutane (the expected product) and 2-chloro-2,3-dimethylbutane (the unexpected product). Again, the unexpected product is the major product of the reaction.

$$CH_3C(CH_3)_2{-}CH{=}CH_2 + HCl \longrightarrow CH_3C(CH_3)_2{-}CHClCH_3 + CH_3CCl(CH_3){-}CH(CH_3)CH_3$$

3,3-dimethyl-1-butene; 3-chloro-2,2-dimethylbutane (minor product); 2-chloro-2,3-dimethylbutane (major product)

In each reaction, the unexpected product results from a *rearrangement* of the carbocation intermediate. Not all carbocations rearrange. *Carbocations rearrange only if they become more stable as a result of the rearrangement.*

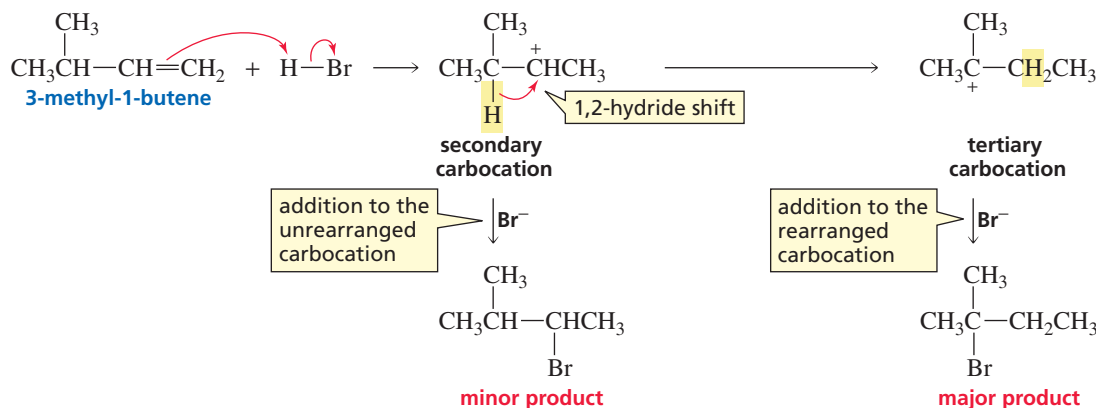
Let's now look at the carbocations that are formed in the preceding reactions to see why they rearrange. In the first reaction, a *secondary* carbocation is formed initially. However, the secondary carbocation has a hydrogen that can shift with its pair of electrons to the adjacent positively charged carbon, creating a more stable *tertiary* carbocation.

Carbocations rearrange if they become more stable as a result of the rearrangement.

$$CH_3CH(CH_3){-}CH{=}CH_2 + H{-}Br \longrightarrow CH_3C(CH_3)(H){-}\overset{+}{C}HCH_3 \xrightarrow{\text{1,2-hydride shift}} CH_3\overset{+}{C}(CH_3){-}CH_2CH_3$$

3-methyl-1-butene; secondary carbocation; tertiary carbocation

addition to the unrearranged carbocation: secondary carbocation $\xrightarrow{Br^-}$ $CH_3CH(CH_3){-}CHBrCH_3$ (minor product)

addition to the rearranged carbocation: tertiary carbocation $\xrightarrow{Br^-}$ $CH_3CBr(CH_3){-}CH_2CH_3$ (major product)

Because a hydrogen shifts with its pair of electrons, the rearrangement is called a hydride shift. (Recall that $H:^-$ is a hydride ion.) More specifically, it is called a **1,2-hydride shift** because the hydride ion moves from one carbon to an *adjacent* carbon.

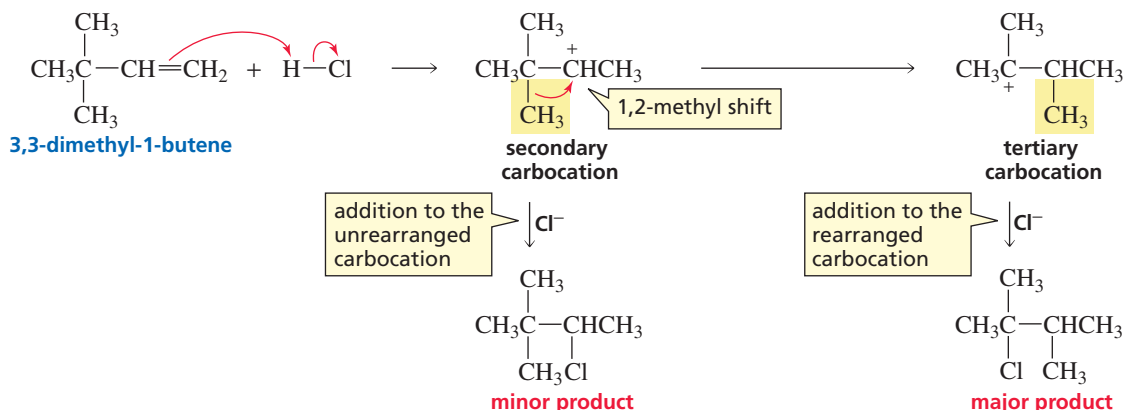
As a result of the **carbocation rearrangement,** two alkyl halides are formed, one from adding the nucleophile to the unrearranged carbocation and one from adding the nucleophile to the rearranged carbocation. *The major product results from adding the nucleophile to the rearranged carbocation.*

In the second reaction, again a *secondary* carbocation is formed initially. Then one of the methyl groups, with its pair of electrons, shifts to the adjacent positively charged carbon to form a more stable *tertiary* carbocation. This kind of rearrangement is called a **1,2-methyl shift**—the methyl group moves with its electrons from one carbon to an *adjacent* carbon. Again, the major product is the one formed by adding the nucleophile to the rearranged carbocation.

$$CH_3C(CH_3)_2-CH{=}CH_2 + H-Cl \longrightarrow CH_3C(CH_3)_2-\overset{+}{C}HCH_3 \longrightarrow CH_3\overset{+}{C}(CH_3)-CH(CH_3)CH_3$$

3,3-dimethyl-1-butene; secondary carbocation; 1,2-methyl shift; tertiary carbocation

addition to the unrearranged carbocation (Cl^-): $CH_3C(CH_3)_2-CHClCH_3$ — minor product

addition to the rearranged carbocation (Cl^-): $CH_3CCl(CH_3)-CH(CH_3)CH_3$ — major product

PROBLEM 8 Solved

Which of the following carbocations would be expected to rearrange?

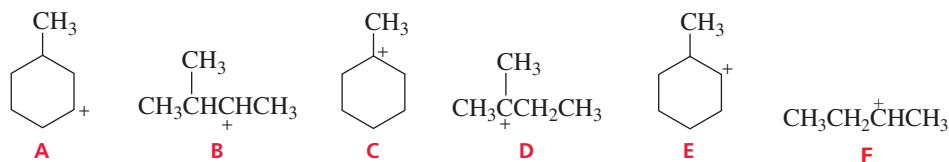
A: 2-methylcyclohexyl cation (+ on carbon adjacent to the CH_3-bearing carbon)

B: $CH_3CH(CH_3)\overset{+}{C}HCH_3$

C: 1-methylcyclohexyl cation (CH_3 and + on the same carbon)

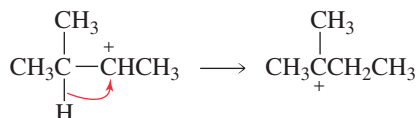
D: $CH_3\overset{+}{C}(CH_3)CH_2CH_3$

E: 2-methylcyclohexyl cation (+ on carbon adjacent to the CH_3-bearing carbon)

F: $CH_3CH_2\overset{+}{C}HCH_3$

Solution

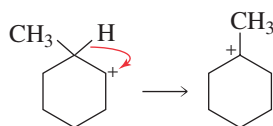
A is secondary carbocation. It will not rearrange because a 1,2-hydride shift would convert it to a different secondary carbocation, so there is no energetic advantage to the rearrangement.

B is a secondary carbocation. It will rearrange because a 1,2-hydride shift converts it to a tertiary carbocation.

$$CH_3C(CH_3)(H)-\overset{+}{C}HCH_3 \longrightarrow CH_3\overset{+}{C}(CH_3)CH_2CH_3$$

C is a tertiary carbocation. It will not rearrange because its stability cannot be improved by rearrangement.

D is a tertiary carbocation. It will not rearrange because its stability cannot be improved by rearrangement.

E is secondary carbocation. It will rearrange because a 1,2-hydride shift converts it to a tertiary carbocation.

$$\text{2-methylcyclohexyl cation } (CH_3, H) \longrightarrow \text{1-methylcyclohexyl cation } (CH_3, +)$$

F is a secondary carbocation. It will not rearrange because rearrangement would form another secondary carbocation.

6.5 THE ADDITION OF WATER TO AN ALKENE

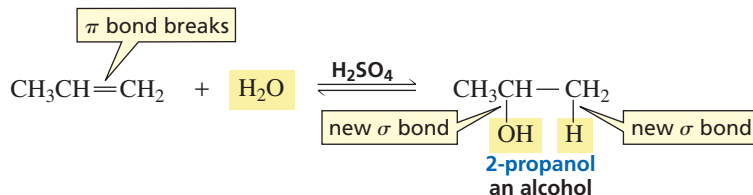
An alkene does not react with water, because there is no electrophile present to start the reaction by adding to the alkene. The O—H bonds of water are too strong—water is too weakly acidic—to allow the hydrogen to act as an electrophile.

$$CH_3CH{=}CH_2 \quad + \quad H_2O \quad \longrightarrow \quad \text{no reaction}$$

If an acid (the acid used most often is H_2SO_4) is added to the solution, then a reaction will occur because the acid provides the electrophile. The product of the reaction is an *alcohol.* The addition of water to a molecule is called **hydration,** so we can say that an alkene will be *hydrated* in the presence of water and acid.

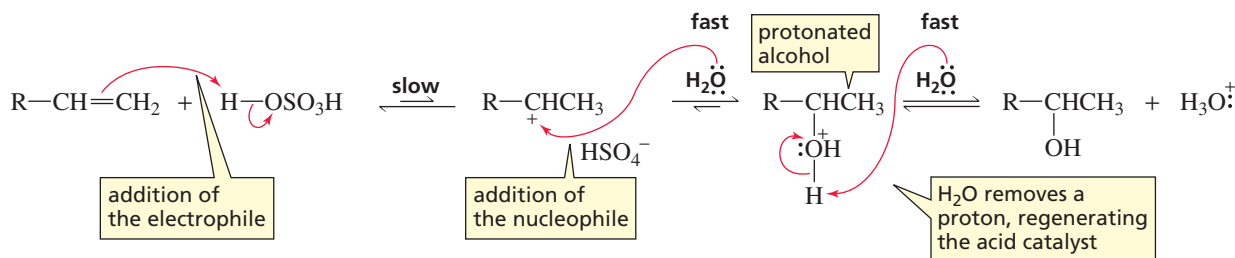
$$CH_3CH{=}CH_2 \quad + \quad H_2O \quad \xrightleftharpoons{H_2SO_4} \quad CH_3\underset{\displaystyle OH}{\underset{|}{C}H}-\underset{\displaystyle H}{\underset{|}{C}H_2}$$

π bond breaks; new σ bond; new σ bond

2-propanol
an alcohol

When you look at the *mechanism for the acid-catalyzed addition of water to an alkene*, notice that the first two steps are the same (except for the nucleophile employed) as the two steps of the *mechanism for the addition of a hydrogen halide to an alkene* (Section 6.1).

MECHANISM FOR THE ACID-CATALYZED ADDITION OF WATER TO AN ALKENE

$$R-CH{=}CH_2 + H-OSO_3H \xrightleftharpoons{\text{slow}} R-\overset{+}{C}HCH_3 + HSO_4^- \xrightleftharpoons[\text{fast}]{H_2\ddot{O}} R-CH\underset{\displaystyle \overset{+}{:}\!OH\text{—}H}{\underset{|}{C}H_3} \xrightleftharpoons[\text{fast}]{H_2\ddot{O}} R-\underset{\displaystyle OH}{\underset{|}{C}H}CH_3 + H_3\overset{+}{O}:$$

addition of the electrophile; addition of the nucleophile; protonated alcohol; H_2O removes a proton, regenerating the acid catalyst

- H^+ (an electrophile) adds to the sp^2 carbon of the alkene (a nucleophile) that is bonded to the most hydrogens.
- H_2O (a nucleophile) adds to the carbocation (an electrophile), forming a protonated alcohol.
- The protonated alcohol loses a proton because the pH of the solution is greater than the pK_a of the protonated alcohol (Section 2.10). (We have seen that protonated alcohols are very strong acids; Section 2.6.)

Thus, the overall reaction is the addition of an electrophile to the sp^2 carbon bonded to the most hydrogens and addition of a nucleophile to the other sp^2 carbon.

As we saw in Section 5.9, the addition of the electrophile to the alkene is relatively slow, whereas the subsequent addition of the nucleophile to the carbocation occurs rapidly. The reaction of the carbocation with a nucleophile is so fast that the carbocation combines with whatever nucleophile it collides with first. Notice that there are two nucleophiles in solution, water and HSO_4^- (the conjugate base of the acid used to start the reaction).* Because the concentration of water is greater than the concentration of HSO_4^-, the carbocation is more likely to collide with water. The final product of the addition reaction, therefore, is an alcohol.

Do not memorize the products obtained from the reactions of alkenes. Instead, for each reaction, ask yourself, "What is the electrophile?" and "What nucleophile is present in the greatest concentration?"

H_2SO_4 catalyzes the hydration reaction. We have seen that a catalyst increases the rate of a reaction but is not consumed during the course of the reaction (Section 5.10). Thus, the proton adds to the alkene in the first step, but is returned to the reaction mixture in the

*HO^- cannot be a nucleophile in this reaction because there is no appreciable concentration of HO^- in an acidic solution.

final step. Overall, then, a proton is not consumed. Because the catalyst employed in the hydration of an alkene is an acid, hydration is called an **acid-catalyzed reaction.**

Remember that catalysts increase the reaction rate by decreasing the free energy of activation, but they do *not* affect the equilibrium constant of the reaction (Section 5.10). In other words, a catalyst increases the *rate* at which a product is formed but does not affect the *amount* of product formed after the reaction has reached equilibrium.

PROBLEM 9♦

Answer the following questions about the mechanism for the acid-catalyzed hydration of an alkene:

a. How many transition states are there?
b. How many intermediates are there?
c. Which step in the forward direction has the smallest rate constant?

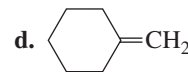
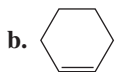
PROBLEM 10♦

What is the major product obtained from the acid-catalyzed hydration of each of the following alkenes?

a. $CH_3CH_2CH_2CH{=}CH_2$

b. (cyclohexene)

c. $CH_3CH_2CH_2CH{=}CHCH_3$

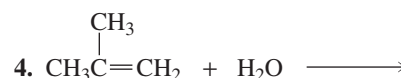
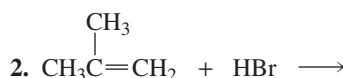
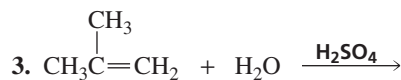
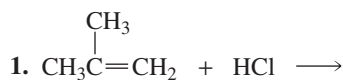
d. (cyclohexane ring)$=CH_2$

PROBLEM 11

a. What is the major product of each of the following reactions?

1. $CH_3C(CH_3){=}CH_2 + HCl \longrightarrow$

2. $CH_3C(CH_3){=}CH_2 + HBr \longrightarrow$

3. $CH_3C(CH_3){=}CH_2 + H_2O \xrightarrow{H_2SO_4}$

4. $CH_3C(CH_3){=}CH_2 + H_2O \longrightarrow$

b. What do the first three reactions have in common?
c. How do the first three reactions differ?

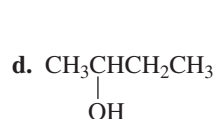
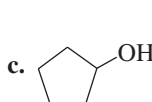
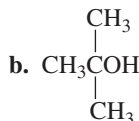
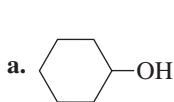
PROBLEM 12

How could the following compounds be prepared, using an alkene as one of the starting materials?

a. (cyclohexane ring)—OH

b. $CH_3C(CH_3)_2OH$ (CH_3COH with CH_3 above and CH_3 below)

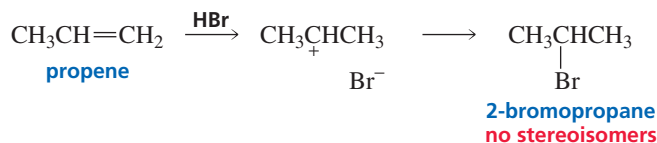
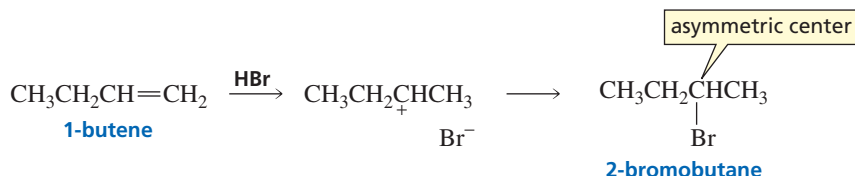
c. (cyclopentane ring)—OH

d. $CH_3CHCH_2CH_3$ with OH on C-2

6.6 THE STEREOCHEMISTRY OF ALKENE REACTIONS

Now that you are familiar with stereoisomers (Chapter 4) *and* with electrophilic addition reactions, we can combine the two topics and look at the stereochemistry of these reactions. In other words, we will look at the stereoisomers that are formed in the electrophilic addition reactions that you learned about in this chapter.

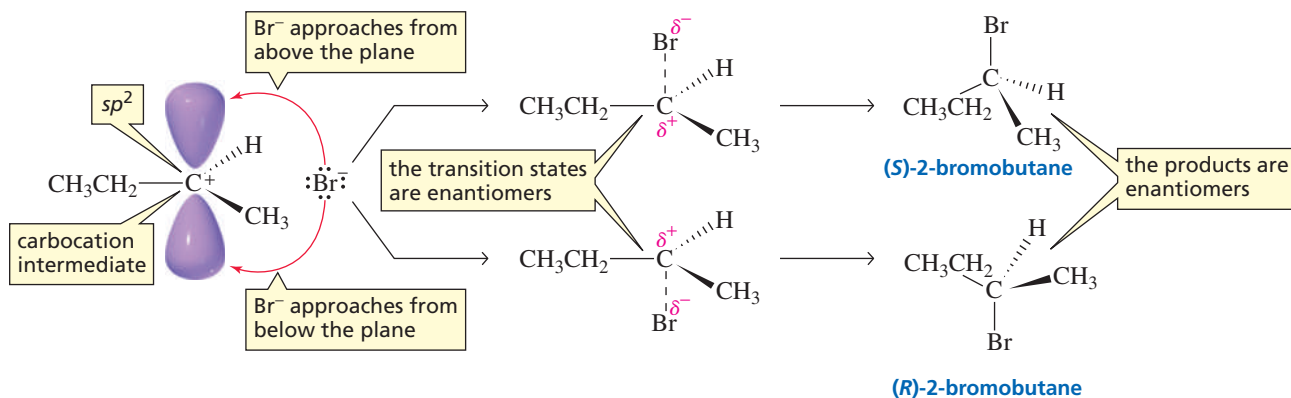
We have seen that when an alkene reacts with an electrophilic reagent such as HBr, the major product of the addition reaction is the one obtained by adding the electrophile (H^+) to the sp^2 carbon bonded to the most hydrogens and adding the nucleophile (Br^-) to the other sp^2 carbon (Section 6.3). Thus, the major product obtained from the following reaction is 2-bromopropane. This product does not have an asymmetric center, so it does not have stereoisomers. Therefore, we do not have to be concerned with the stereochemistry of the reaction.

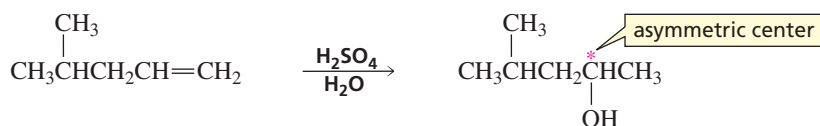
$$CH_3CH{=}CH_2 \xrightarrow{HBr} CH_3\overset{+}{C}HCH_3 \;\; Br^- \longrightarrow CH_3CH(Br)CH_3$$

propene — 2-bromopropane, no stereoisomers

The following reaction forms a product with an asymmetric center, so now we have to be concerned with the stereochemistry of this reaction. What is the configuration of the product? In other words, do we get the *R* enantiomer, the *S* enantiomer, or both enantiomers?

$$CH_3CH_2CH{=}CH_2 \xrightarrow{HBr} CH_3CH_2\overset{+}{C}HCH_3 \;\; Br^- \longrightarrow CH_3CH_2CH(Br)CH_3$$

1-butene — 2-bromobutane (asymmetric center)

When a reactant that does *not* have an asymmetric center undergoes a reaction that forms a product with *one* asymmetric center, the product will always be a racemic mixture. For example, the reaction of 1-butene with HBr that we just looked at forms identical amounts of (*R*)-2-bromobutane and (*S*)-2-bromobutane. Why is this so?

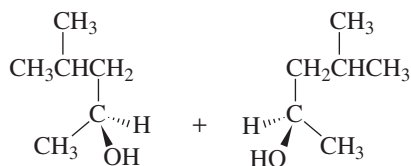
The three groups bonded to the sp^2 carbon of the carbocation intermediate formed when H^+ adds to the alkene lie in a plane (Section 1.10). When the bromide ion approaches the intermediate from above the plane, one enantiomer is formed; when it approaches from below the plane, the other enantiomer is formed. Because the bromide ion has equal access to both sides of the plane, identical amounts of the *R* and *S* enantiomers are formed (Figure 6.3).

▲ **Figure 6.3**
Because the products of the reaction are enantiomers, the transition states that lead to the products are also enantiomers. Thus, the two transition states have the same stability, so the two products will be formed at the same rate. The product, therefore, is a racemic mixture.

A racemic mixture is formed by any reaction that forms a product with an asymmetric center from a reactant that does not have an asymmetric center. Thus, the product of the following reaction is a racemic mixture.

When a reactant that does not have an asymmetric center forms a product with *one* asymmetric center, the product will always be a racemic mixture.

$$CH_3CH(CH_3)CH_2CH{=}CH_2 \xrightarrow[H_2O]{H_2SO_4} CH_3CH(CH_3)CH_2\overset{*}{C}H(OH)CH_3$$

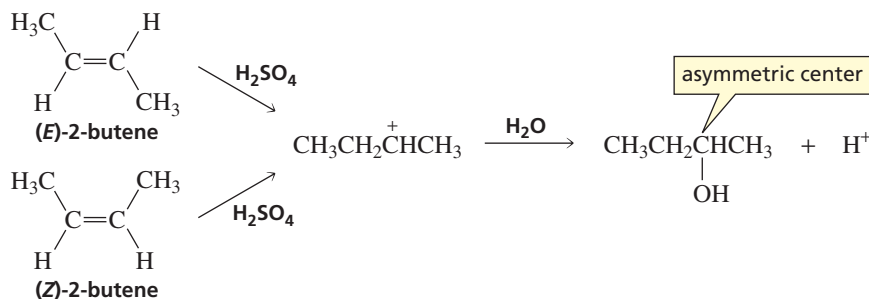
(asymmetric center)

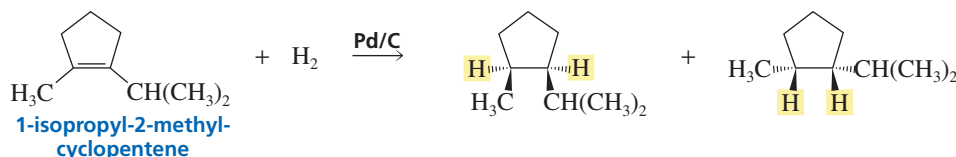
The reaction products will have the configurations shown here.

$$\text{(CH}_3)_2\text{CHCH}_2\text{–C(H)(CH}_3\text{)(OH)} \; + \; \text{(CH}_3)_2\text{CHCH}_2\text{–C(H)(CH}_3\text{)(OH)}$$

Notice that the same product is obtained from the *E* and *Z* stereoisomers of an alkene because they both form the same carbocation. Because this reaction forms a new asymmetric center, the product will be a racemic mixture.

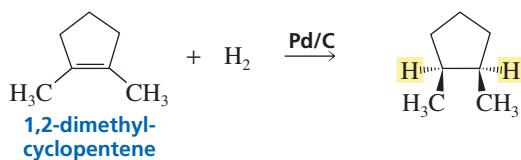
(*E*)-2-butene $\xrightarrow{H_2SO_4}$ $CH_3CH_2\overset{+}{C}HCH_3$ $\xrightarrow{H_2O}$ $CH_3CH_2CH(OH)CH_3$ + H^+

(*Z*)-2-butene $\xrightarrow{H_2SO_4}$ $CH_3CH_2\overset{+}{C}HCH_3$

asymmetric center

We have seen that in a catalytic hydrogenation reaction, the alkene sits on the surface of a metal catalyst onto which H_2 has been absorbed (Figure 5.3). As a result, both hydrogen atoms add to the same side of the double bond. Therefore, if the alkene is cyclic, the addition of H_2 will form the cis stereoisomers since the two hydrogens add to the same side of the double bond. Because the hydrogens can approach the double bond from the top or from the bottom, two stereoisomers are formed. The product is a racemic mixture. You can see that the two products are enantiomers (nonsuperimposable mirror images) if you turn one of them upside down.

1-isopropyl-2-methyl-cyclopentene + H_2 $\xrightarrow{Pd/C}$ (cis product: H, H; H_3C, $CH(CH_3)_2$) + (cis product: H_3C, $CH(CH_3)_2$; H, H)

Notice that, in the reaction we just looked at, two asymmetric centers are formed in the product. We have seen that a compound with two asymmetric centers can have as many as four stereoisomers (Section 4.10). This reaction forms only two stereoisomers because both hydrogens have to add to the same side of the double bond. The other two stereoisomers could be obtained only if the two hydrogens could add to opposite sides of the double bond.

The following reaction forms only one stereoisomer. Each of the two asymmetric centers in the product is bonded to the same four substituents. Thus, the product is a meso compound. Recall that a meso compound is superimposable on its mirror image (Section 4.12), so the reaction forms a single stereoisomer.

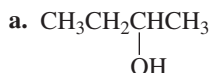
1,2-dimethyl-cyclopentene + H_2 $\xrightarrow{Pd/C}$ (cis product: H, H; H_3C, CH_3)

PROBLEM-SOLVING STRATEGY

Predicting the Stereoisomers Obtained from the Addition Reactions of Alkenes

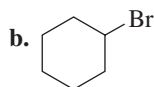
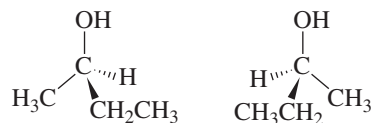
What stereoisomers are obtained from the following reactions?

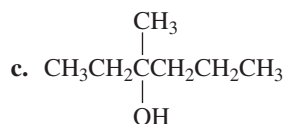
a. 1-butene + H_2O + H_2SO_4
b. cyclohexene + HBr
c. (*E*)-3-methyl-2-hexene + H_2O + H_2SO_4
d. (*Z*)-3-methyl-2-hexene + H_2O + H_2SO_4

Start by drawing the product without regard to its configuration to check whether the reaction has created any asymmetric centers. Then determine the stereoisomers of the products. Let's start with part **a.**

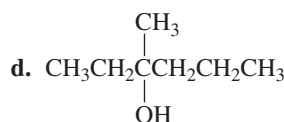
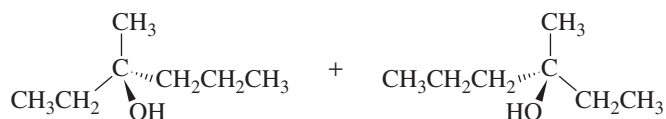
a. $CH_3CH_2CH(OH)CH_3$

The product has one asymmetric center, so equal amounts of the *R* and *S* enantiomers will be obtained.

OH — C(H)(H$_3$C)(CH$_2$CH$_3$)   OH — C(H)(CH$_3$CH$_2$)(CH$_3$)

b. (bromocyclohexane: cyclohexane ring with Br)

The product does not have an asymmetric center, so it has no stereoisomers.

c. $CH_3CH_2C(CH_3)(OH)CH_2CH_2CH_3$

The product has an asymmetric center, so equal amounts of the *R* and *S* enantiomers will be obtained.

CH_3CH_2–C(CH_3)(OH)–$CH_2CH_2CH_3$ + $CH_3CH_2CH_2$–C(CH_3)(HO)–CH_2CH_3

d. $CH_3CH_2C(CH_3)(OH)CH_2CH_2CH_3$

The same stereoisomers that are formed in part **c** will be obtained. Recall that *E* and *Z* stereoisomers form the same product because they form the same carbocation.

Now use the strategy you have just learned to solve Problems 13 and 14.

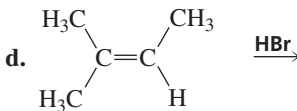
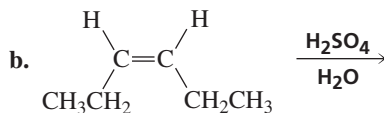
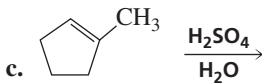
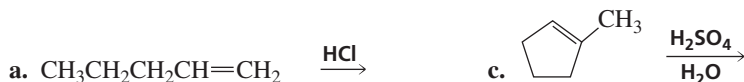
PROBLEM 13

What stereoisomers are obtained from each of the following reactions?

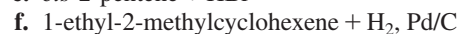
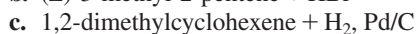
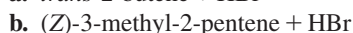
a. $CH_3CH_2CH_2CH{=}CH_2 \xrightarrow{HCl}$

c. 1-methylcyclopentene (CH_3) $\xrightarrow[H_2O]{H_2SO_4}$

b. (H)(CH$_3$CH$_2$)C=C(H)(CH$_2$CH$_3$) $\xrightarrow[H_2O]{H_2SO_4}$

d. (H$_3$C)(H$_3$C)C=C(CH$_3$)(H) $\xrightarrow{HBr}$

PROBLEM 14

What stereoisomers are obtained from the following reactions?

a. *trans*-2-butene + HBr
b. (*Z*)-3-methyl-2-pentene + HBr
c. 1,2-dimethylcyclohexene + H_2, Pd/C
d. *cis*-3-hexene + HBr
e. *cis*-2-pentene + HBr
f. 1-ethyl-2-methylcyclohexene + H_2, Pd/C

6.7 THE STEREOCHEMISTRY OF ENZYME-CATALYZED REACTIONS

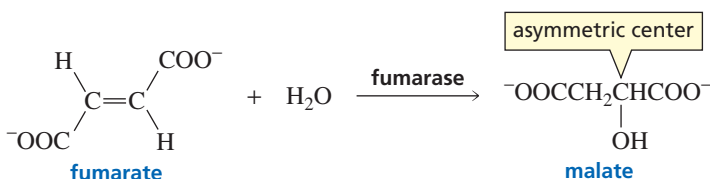
The chemistry associated with living organisms is called **biochemistry.** When you study biochemistry, you study the structures and functions of the molecules found in the biological world, and the reactions involved in the synthesis and degradation of

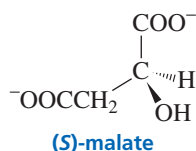
these molecules. Because the compounds in living organisms are organic compounds, it is not surprising that many of the reactions encountered in organic chemistry also occur in cells.

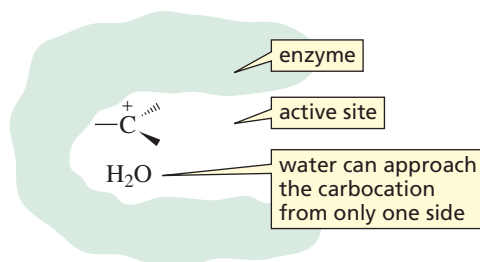
Reactions that occur in biological systems are catalyzed by proteins called **enzymes** (Section 5.11). We have seen that when an alkene reacts with reagents such as HBr or H_2SO_4/H_2O and forms a product with an asymmetric center, the product is a racemic mixture. However, when the reaction is catalyzed by an enzyme, only one stereoisomer is formed.

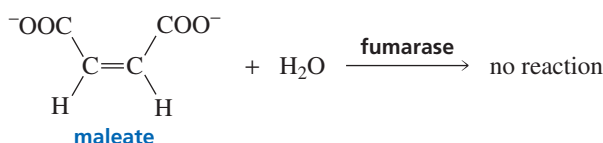
For example, the enzyme fumarase catalyzes the addition of water to fumarate to form malate, a compound with an asymmetric center.

When an enzyme catalyzes a reaction that forms a product with an asymmetric center, only one stereoisomer is formed.

fumarate + H_2O —fumarase→ $^{-}OOCCH_2CHCOO^{-}$ (OH on CH) malate (asymmetric center)

The reaction forms only (*S*)-malate; the *R* enantiomer is not formed.

(*S*)-malate

An enzyme-catalyzed reaction forms only one stereoisomer because an enzyme's binding site can restrict delivery of the reagents to only one side of the reactant.

enzyme; active site; water can approach the carbocation from only one side

Also, an enzyme typically catalyzes the reaction of only one stereoisomer. For example, fumarase catalyzes the addition of water to fumarate (the trans isomer just shown) but not to maleate (the cis isomer).

maleate + H_2O —fumarase→ no reaction

An enzyme is able to differentiate between the two stereoisomers because only one of them has the structure that allows it to fit into the enzyme's active site where the reaction takes place (Section 5.11).

6.8 ENANTIOMERS CAN BE DISTINGUISHED BY BIOLOGICAL MOLECULES

Enzymes, like receptors (Section 4.13), can tell the difference between enantiomers because enzymes and receptors are proteins, and proteins are chiral molecules.

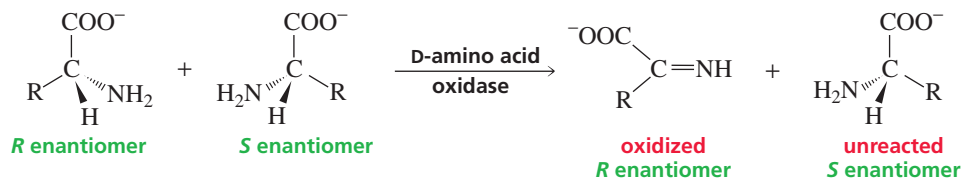
Enzymes

An achiral reagent, such as hydroxide ion, cannot distinguish between enantiomers. Thus, it reacts with (*R*)-2-bromobutane at the same rate that it reacts with (*S*)-2-bromobutane.

Because an enzyme is *chiral*, not only can it distinguish between cis–trans isomers, such as maleate and fumarate (Section 6.6), but it can also distinguish between enantiomers and catalyze the reaction of only one of them.

Chemists can use an enzyme's ability to distinguish between enantiomers to separate them. For example, the enzyme D-amino acid oxidase catalyzes only the oxidation of the *R* enantiomer but leaves the *S* enantiomer unchanged. The oxidized product of the enzyme-catalyzed reaction can be easily separated from the unreacted enantiomer because they are different compounds.

COO^- / R—C—NH_2 / H + COO^- / H_2N—C—R / H $\xrightarrow{\text{D-amino acid oxidase}}$ ^-OOC—C(=NH)—R + COO^- / H_2N—C—R / H

R enantiomer — *S* enantiomer — oxidized *R* enantiomer — unreacted *S* enantiomer

An achiral reagent reacts identically with both enantiomers. A sock, which is achiral, fits on either foot.

A chiral reagent reacts differently with each enantiomer. A shoe, which is chiral, fits on only one foot.

An enzyme is able to differentiate between enantiomers and between cis and trans isomers, because its binding site is chiral. Therefore, the enzyme will bind only the stereoisomer whose substituents are in the correct positions to interact with the substituents in the chiral binding site (Figure 4.8).

Like a right-handed glove, which fits only the right hand, an enzyme forms only one stereoisomer and reacts with only one stereoisomer.

PROBLEM 15♦

a. What would be the product of the reaction of fumarate and H_2O if H_2SO_4 were used as a catalyst instead of fumarase?

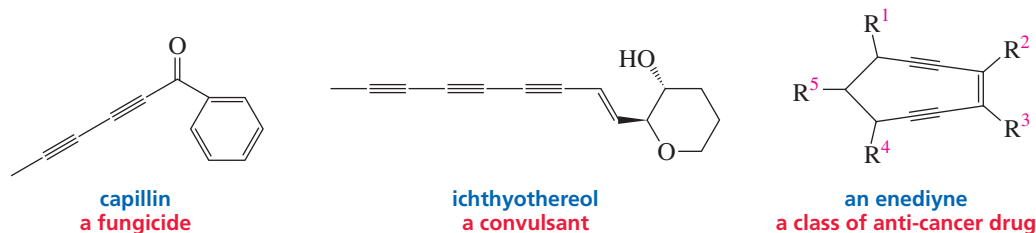
b. What would be the product of the reaction of maleate and H_2O if H_2SO_4 were used as a catalyst instead of fumarase?

6.9 AN INTRODUCTION TO ALKYNES

An **alkyne** is a hydrocarbon that contains a carbon–carbon triple bond. Relatively few alkynes are found in nature. Examples include capillin, which has fungicidal activity, and ichthyothereol, a convulsant used by the indigenous people of the Amazon for poisoned arrowheads.

capillin
a fungicide

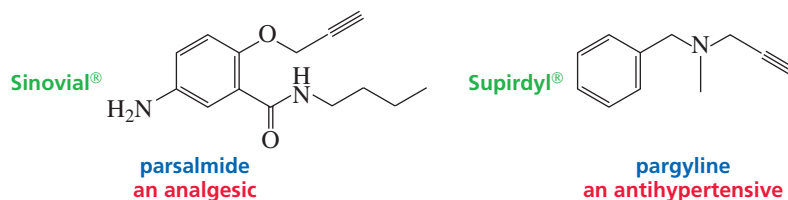
ichthyothereol
a convulsant

an enediyne
a class of anti-cancer drug

A class of naturally occurring compounds called enediynes has been found to have powerful anticancer properties because they are able to cleave DNA. (You will see how they do this in Chapter 14, Problem 22.) All enediynes have a nine- or ten-membered ring that contains two triple bonds separated by a double bond. One of the first enediynes approved for clinical use is used to treat acute myeloid leukemia. Several others are currently in clinical trials (see the box that appears later in this section).

Other drugs on the market that contain an alkyne functional group are not naturally occurring compounds; they exist only because chemists have been able to synthesize them. Their trade names are shown in green. Trade names are always capitalized;

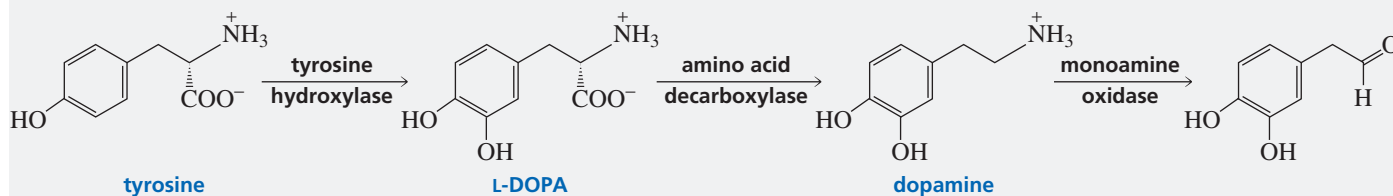
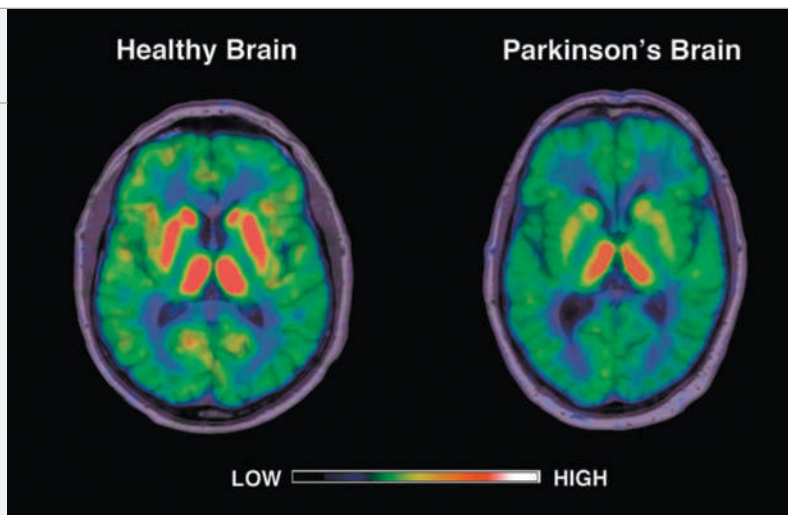
only the company that holds the patent for a product can use the product's trade name for commercial purposes.

Sinovial® parsalmide an analgesic

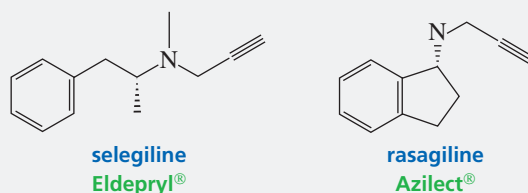
Supirdyl® pargyline an antihypertensive

Synthetic Alkynes Are Used to Treat Parkinson's Disease

Parkinson's disease is a degenerative condition characterized by tremors. It is caused by the destruction of cells in the *substantia nigra*, a crescent-shaped region in the midbrain. These are the cells that release dopamine, the neurotransmitter that plays an important role in movement, muscle control, and balance. A neurotransmitter is a compound used to communicate between brain cells.

Dopamine is synthesized from tyrosine (one of the 20 common amino acids; Section 17.1). Ideally, Parkinson's disease could be treated by giving the patient dopamine. Unfortunately, dopamine is not polar enough to cross the blood–brain barrier. Therefore, L-DOPA, its immediate precursor, is the drug of choice, but it ceases to control the disease's symptoms after it has been used for a while.

tyrosine —(tyrosine hydroxylase)→ L-DOPA —(amino acid decarboxylase)→ dopamine —(monoamine oxidase)→

Dopamine is oxidized in the body by an enzyme called monoamine oxidase. Two drugs, each containing a C≡CH group, have been developed that inhibit this enzyme, thus preventing the oxidation of dopamine and thereby increasing its availability in the brain. Both drugs have structures similar to that of dopamine, so they are able to bind to the enzyme's active site. (Recall that enzymes recognize their substrates by their shape; Sections 6.6 and 6.7.) Because these drugs form covalent bonds with groups at the enzyme's active site, they become permanently attached to the active site, thus preventing the enzyme from binding dopamine. Patients on these drugs continue to take L-DOPA, but now this drug can be taken at longer intervals and it can control the disease's symptoms for a longer period of time.

selegiline Eldepryl®

rasagiline Azilect®

Selegiline was approved by the FDA first, but one of the compounds to which it is metabolized has a structure similar to that of methamphetamine (the street drug known as "speed"; page 169). So, some patients taking the drug experience psychiatric and cardiac effects. These side effects have not been found in patients taking rasagiline.

Notice that the name of most enzymes ends in "ase," preceded by an indication of what reaction the enzyme catalyzes. Thus, tyrosine hydroxylase puts an OH group on tyrosine, amino acid decarboxylase removes a carboxyl (COO^-) group from an amino acid (or, in this case, from a compound similar to an amino acid), and monoamine oxidase oxidizes an amine.

Why Are Drugs So Expensive?

The average cost of launching a new drug is \$1.2 billion. The manufacturer has to recover this cost quickly because the patent has to be filed as soon as the drug is first discovered. Although a patent is good for 20 years, it takes an average of 12 years to bring a drug to market after its initial discovery, so the patent protects the discoverer of the drug for an average of 8 years. It is only during the eight years of patent protection that drug sales can provide the income needed to cover the initial costs as well as to pay for research on new drugs.

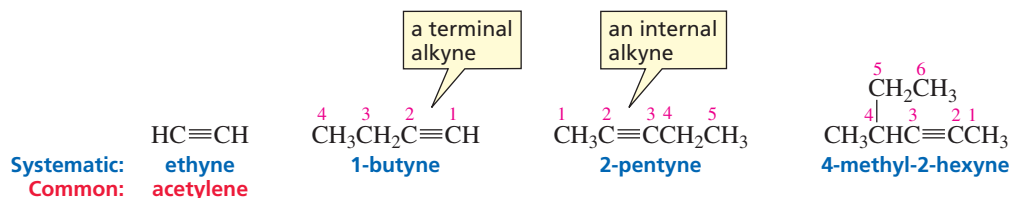
Why does it cost so much to develop a new drug? First of all, the Food and Drug Administration (FDA) has high standards that must be met before a drug is approved for a particular use. An important factor leading to the high price of many drugs is the low rate of success in progressing from the initial concept to an approved product. In fact, only 1 or 2 of every 100 compounds tested become lead compounds. A lead compound is a compound that shows promise of becoming a drug. Chemists modify the structure of a lead compound to see if doing so improves its likelihood of becoming a drug. For every 100 structural modifications of a lead compound, only 1 is worthy of further study. For every 10,000 compounds evaluated in animal studies, only 10 will get to clinical trials.

Clinical trials consist of three phases. Phase I evaluates the effectiveness, safety, side effects, and dosage levels in up to 100 healthy volunteers; phase II investigates the effectiveness, safety, and side effects in 100 to 500 volunteers who have the condition the drug is meant to treat; and phase III establishes the effectiveness and appropriate dosage of the drug and monitors adverse reactions in several thousand volunteer patients. For every 10 compounds that enter clinical trials, only 1 satisfies the increasingly stringent requirements to become a marketable drug.

6.10 THE NOMENCLATURE OF ALKYNES

The systematic name of an alkyne is obtained by replacing the "ane" ending of the alkane name with "yne." Analogous to the way alkenes are named, the longest continuous chain containing the carbon–carbon triple bond is numbered in the direction that gives the functional group suffix as low a number as possible (Section 5.1). If the triple bond is at the end of the chain, the alkyne is classified as a **terminal alkyne.** Alkynes with triple bonds located elsewhere along the chain are **internal alkynes.**

1-hexyne
a terminal alkyne

3-hexyne
an internal alkyne

Acetylene is an unfortunate common name for an alkyne because its "ene" ending is characteristic of a double bond rather than a triple bond.

If counting from either direction leads to the same number for the functional group suffix, the correct systematic name is the one that contains the lowest substituent number. If the compound contains more than one substituent, the substituents are listed in alphabetical order.

3-bromo-2-chloro-4-octyne
not **6-bromo-7-chloro-4-octyne**
because 2 < 6

1-bromo-5-methyl-3-hexyne
not **6-bromo-2-methyl-3-hexyne**
because 1 < 2

A substituent receives the lowest possible number only if there is no functional group suffix, or if counting from either direction leads to the same number for the functional group suffix.

PROBLEM 16♦

Name the following:

Synthetic Alkynes Are Used for Birth Control

Estradiol and progesterone are naturally occurring female hormones. Because of their skeletal ring structures, they are classified as steroids (Section 3.14). Estradiol is responsible for the development of secondary sex characteristics in women—it affects body shape, fat deposition, bones, and joints. Progesterone is critical for the continuation of pregnancy.

estradiol

progesterone

The four compounds shown next are synthetic steroids that are used for birth control; each contains an alkyne functional group. Most birth control pills contain ethinyl estradiol (a compound structurally similar to estradiol) and a compound structurally similar to progesterone (such as norethindrone). Ethinyl estradiol prevents ovulation, whereas norethindrone makes it difficult for a fertilized egg to attach to the wall of the uterus.

HO H H H HO
ethinyl estradiol

HO H H H H O
norethindrone
Aygestin®

N HO H H O
mifepristone
RU-486
Mifegyne®

HO H H H H O
levonorgestrel
Norplant®

Mifepristone and levonorgestrel are also synthetic steroids that contain an alkyne functional group. Mifepristone, also known as RU-486, induces an abortion if taken early in pregnancy. Its name comes from Roussel-Uclaf, the French pharmaceutical company by which it was first synthesized, and from an arbitrary lab serial number. Levonorgestrel is an emergency contraceptive pill. It prevents pregnancy if taken within a few days of conception.

PROBLEM 17♦

Draw the structure for each of the following:

a. 1-chloro-3-hexyne **b.** cyclooctyne **c.** 4,4-dimethyl-1-pentyne

PROBLEM 18

Draw the structures for and name the seven alkynes with molecular formula C_6H_{10}.

PROBLEM 19♦

Name the following:

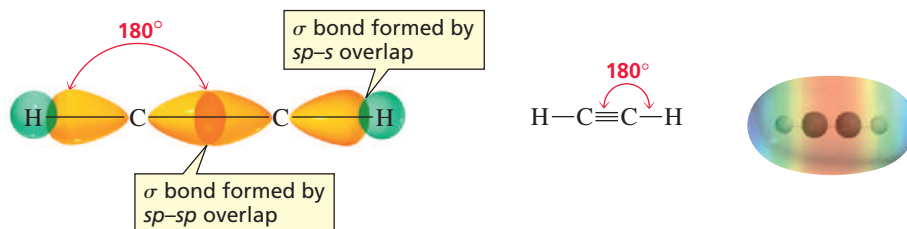
a. $BrCH_2CH_2C{\equiv}CCH_3$ **b.** $CH_3CH_2\underset{\large Br}{CH}C{\equiv}CCH_2\underset{\large Cl}{CH}CH_3$ **c.** $CH_3CH_2\underset{\large CH_2CH_2CH_3}{CH}C{\equiv}CH$

PROBLEM 20♦

Name the following:

a. **b.** **c.** Br

6.11 THE STRUCTURE OF ALKYNES

The structure of ethyne was discussed in Section 1.9, where we saw that each carbon is *sp* hybridized. As a result, each carbon has two *sp* orbitals and two *p* orbitals. One *sp* orbital overlaps the *s* orbital of a hydrogen, and the other overlaps an *sp* orbital of the other carbon. (The small lobes of the *sp* orbitals are not shown.) Because the *sp* orbitals are oriented as far from each other as possible to minimize electron repulsion, ethyne is a linear molecule with bond angles of 180°.

Other alkynes have structures similar to that of ethyne. Recall that the triple bond is formed by each of the two *p* orbitals on one *sp* carbon overlapping the parallel *p* orbital on the other *sp* carbon to form two π bonds (Figure 6.4). The end result can be thought of as a cylinder of electrons wrapped around the σ bond.

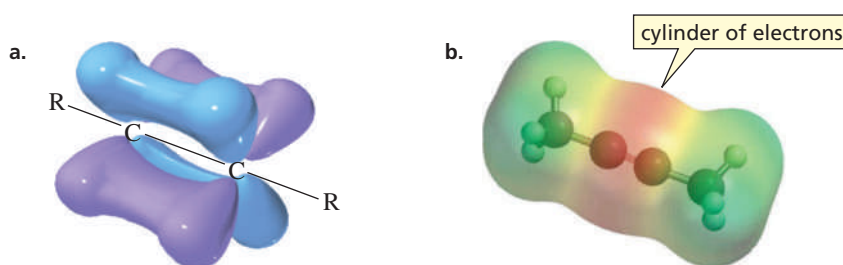



Figure 6.4
(a) Each of the two π bonds of a triple bond is formed by side-to-side overlap of a *p* orbital of one carbon with a parallel *p* orbital of the adjacent carbon.
(b) The electrostatic potential map for 2-butyne shows the cylinder of electrons wrapped around the σ bond.

Also recall that a carbon–carbon triple bond is shorter and stronger than a carbon–carbon double bond, which in turn, is shorter and stronger than a carbon–carbon single bond, and that a π bond is weaker than a σ bond (Section 1.14).

Alkyl groups stabilize alkynes, just as they stabilize alkenes and carbocations (Sections 5.6 and 6.2, respectively). Internal alkynes, therefore, are more stable than terminal alkynes.

A triple bond is composed of a σ bond and two π bonds.

PROBLEM 21♦

What hybrid orbitals are used to form the carbon–carbon σ bond between the highlighted carbons?

a. $CH_3CH{=}CHCH_3$
b. $CH_3CH{=}CHCH_3$
c. $CH_3CH{=}C{=}CH_2$
d. $CH_3C{\equiv}CCH_3$
e. $CH_3C{\equiv}CCH_3$
f. $CH_2{=}CHCH{=}CH_2$
g. $CH_3CH{=}CHCH_2CH_3$
h. $CH_3C{\equiv}CCH_2CH_3$
i. $CH_2{=}CHC{\equiv}CH$

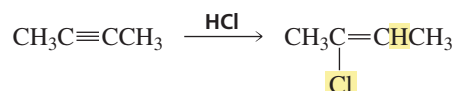
6.12 THE PHYSICAL PROPERTIES OF UNSATURATED HYDROCARBONS

All hydrocarbons—alkanes, alkenes, and alkynes—have similar physical properties. They are all insoluble in water but soluble in nonpolar solvents (Section 3.8). They are less dense than water and, like other homologous series, have boiling points that increase

with increasing molecular weight. Alkynes are more linear than alkenes, causing an alkyne to have stronger van der Waals interactions and, therefore, a higher boiling point than an alkene with the same number of carbons.

6.13 THE ADDITION OF A HYDROGEN HALIDE TO AN ALKYNE

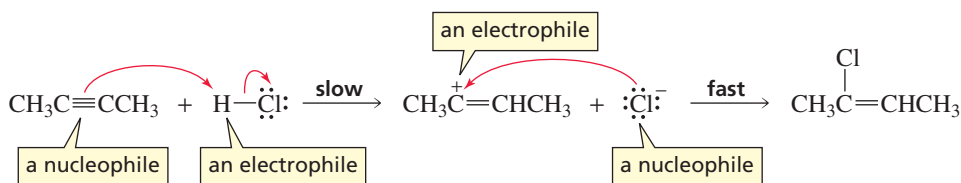
The cloud of electrons completely surrounding the σ bond makes an alkyne an electron-rich molecule. Alkynes therefore are nucleophiles, so they react with electrophiles. Thus alkynes, like alkenes, undergo *electrophilic addition reactions* because of their relatively weak π bonds. The same reagents that add to alkenes also add to alkynes. For example, the addition of hydrogen chloride to an alkyne forms a chloro-substituted alkene.

$$CH_3C{\equiv}CCH_3 \xrightarrow{\text{HCl}} CH_3\underset{\displaystyle Cl}{\underset{|}{C}}{=}CHCH_3$$

Moreover, the mechanism for electrophilic addition to an alkyne is similar to the mechanism for electrophilic addition to an alkene. For example, compare the mechanism for the addition of a hydrogen halide to an alkene shown in Sections 5.3 and 6.1 with the mechanism for the addition of a hydrogen halide to an alkyne shown below.

MECHANISM FOR THE ADDITION OF A HYDROGEN HALIDE TO AN ALKYNE

Recall that an arrowhead with a double barb signifies the movement of two electrons.

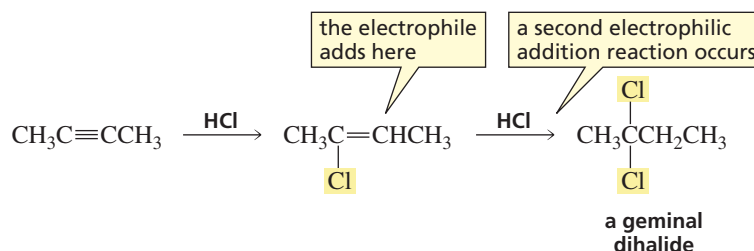
$$CH_3C{\equiv}CCH_3 + H{-}\ddot{\underset{..}{Cl}}\!: \xrightarrow{\text{slow}} CH_3\overset{+}{C}{=}CHCH_3 + :\ddot{\underset{..}{Cl}}\!:^- \xrightarrow{\text{fast}} CH_3\overset{\displaystyle Cl}{\overset{|}{C}}{=}CHCH_3$$

a nucleophile (the alkyne); an electrophile (HCl); an electrophile (the carbocation); a nucleophile (the chloride ion)

- The relatively weak π bond breaks because the π electrons are attracted to the electrophilic proton.
- The positively charged carbocation intermediate reacts rapidly with the negatively charged chloride ion.

The addition reactions of alkynes, however, have a feature that alkenes do not have: because the product of the addition of an electrophilic reagent to an alkyne is an alkene, a second electrophilic addition reaction can occur if *excess* hydrogen halide is present. In the second addition reaction, the electrophile (H^+) adds to the sp^2 carbon bonded to the most hydrogens—as predicted by the rule that governs electrophilic addition reactions (Section 6.3).

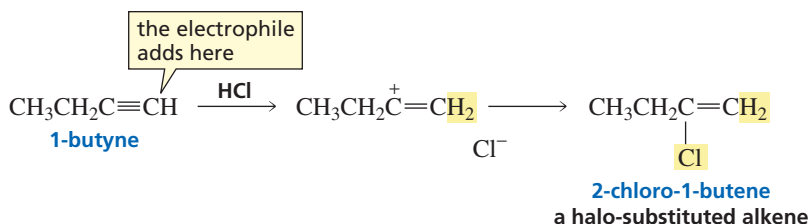
$$CH_3C{\equiv}CCH_3 \xrightarrow{\text{HCl}} CH_3\underset{\displaystyle Cl}{\underset{|}{C}}{=}CHCH_3 \xrightarrow{\text{HCl}} CH_3\overset{\displaystyle Cl}{\overset{|}{\underset{\displaystyle Cl}{\underset{|}{C}}}}CH_2CH_3$$

the electrophile adds here (at the CH of the alkene); a second electrophilic addition reaction occurs

a geminal dihalide

If the alkyne is a *terminal* alkyne, the H^+ will add to the *sp* carbon bonded to the hydrogen, because the *secondary* vinylic cation that results is more stable than the *primary* vinylic cation that would be formed if the H^+ added to the other *sp* carbon. (Recall that alkyl groups stabilize positively charged carbon atoms; see Section 6.2.)

the electrophile adds here

$$CH_3CH_2C{\equiv}CH \xrightarrow{HCl} CH_3CH_2\overset{+}{C}{=}CH_2 \longrightarrow CH_3CH_2\underset{Cl}{C}{=}CH_2$$

1-butyne, Cl^-, 2-chloro-1-butene, a halo-substituted alkene

The electrophile adds to the *sp* carbon that is bonded to the hydrogen.

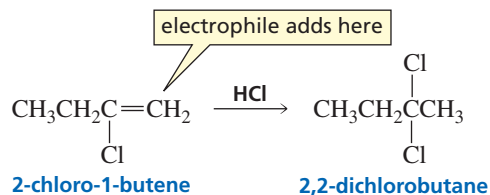
more stable $CH_3CH_2\overset{+}{C}{=}CH_2$ — a secondary vinylic cation

$CH_3CH_2CH{=}\overset{+}{C}H$ less stable — a primary vinylic cation

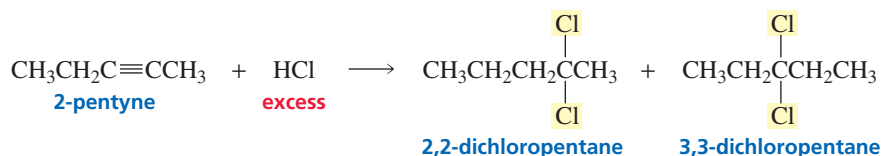
A second addition reaction will take place if excess hydrogen halide is present. Once again, the electrophile (H^+) adds to the sp^2 carbon bonded to the most hydrogens.

electrophile adds here

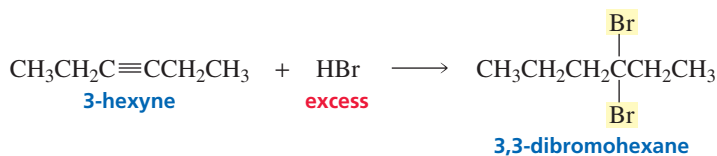
$$CH_3CH_2\underset{Cl}{C}{=}CH_2 \xrightarrow{HCl} CH_3CH_2\overset{Cl}{\underset{Cl}{C}}CH_3$$

2-chloro-1-butene → 2,2-dichlorobutane

Addition of a hydrogen halide to an *internal* alkyne forms two products, because the initial addition of the proton can occur with equal ease to either of the *sp* carbons.

$$CH_3CH_2C{\equiv}CCH_3 + HCl \longrightarrow CH_3CH_2CH_2\overset{Cl}{\underset{Cl}{C}}CH_3 + CH_3CH_2\overset{Cl}{\underset{Cl}{C}}CH_2CH_3$$

2-pentyne, excess (HCl), 2,2-dichloropentane, 3,3-dichloropentane

Note, however, that if the same group is attached to each of the *sp* carbons of the internal alkyne, only one product will be obtained.

$$CH_3CH_2C{\equiv}CCH_2CH_3 + HBr \longrightarrow CH_3CH_2CH_2\overset{Br}{\underset{Br}{C}}CH_2CH_3$$

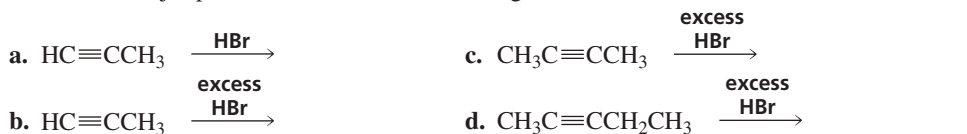
3-hexyne, excess (HBr), 3,3-dibromohexane

PROBLEM 22♦

What is the major product of each of the following reactions?

a. $HC{\equiv}CCH_3 \xrightarrow{HBr}$

b. $HC{\equiv}CCH_3 \xrightarrow{\text{excess HBr}}$

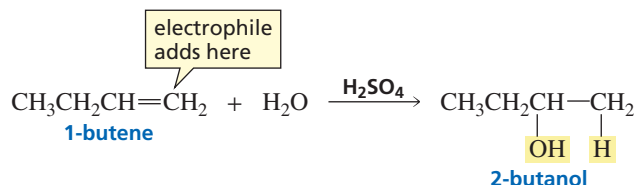
c. $CH_3C{\equiv}CCH_3 \xrightarrow{\text{excess HBr}}$

d. $CH_3C{\equiv}CCH_2CH_3 \xrightarrow{\text{excess HBr}}$

6.14 THE ADDITION OF WATER TO AN ALKYNE

In Section 6.4, we saw that alkenes undergo the acid-catalyzed addition of water. The product of the electrophilic addition reaction is an alcohol.

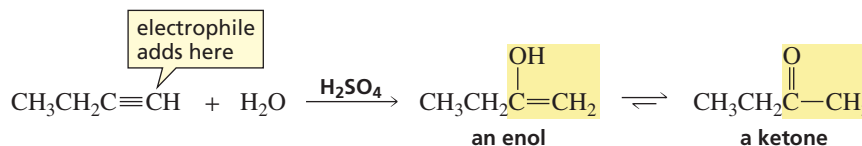
electrophile adds here

$$CH_3CH_2CH{=}CH_2 + H_2O \xrightarrow{H_2SO_4} CH_3CH_2\underset{OH}{C}H{-}\underset{H}{C}H_2$$

1-butene → 2-butanol

Alkynes also undergo the acid-catalyzed addition of water.

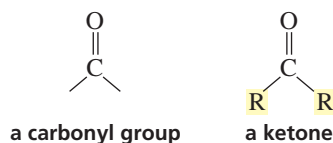
electrophile adds here

$$CH_3CH_2C{\equiv}CH + H_2O \xrightarrow{H_2SO_4} CH_3CH_2\overset{OH}{\overset{|}{C}}{=}CH_2 \rightleftharpoons CH_3CH_2\overset{O}{\overset{\|}{C}}{-}CH_3$$

an enol — a ketone

The initial product of the reaction is an *enol.* An **enol** has a carbon–carbon double bond with an OH group bonded to one of the sp^2 carbons. (The suffix "ene" signifies the double bond, and "ol" signifies the OH group. When the two suffixes are joined, the second *e* of "ene" is dropped to avoid two consecutive vowels, but the word is pronounced as if the second *e* were still there: "ene-ol.")

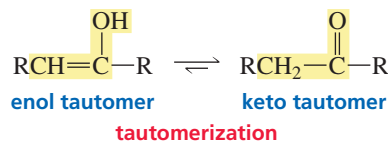
Addition of water to an alkyne forms a ketone.

The enol immediately rearranges to a *ketone*, a compound with the general structure shown below. A carbon doubly bonded to an oxygen is called a **carbonyl** ("carbo-neel") **group;** a **ketone** ("key-tone") is a compound that has two alkyl groups bonded to a carbonyl group.

a carbonyl group — a ketone

A ketone and an enol differ only in the location of a double bond and a hydrogen. A ketone and its corresponding enol are called **keto–enol tautomers. Tautomers** ("taw-toe-mers") are constitutional isomers that are in rapid equilibrium. The keto tautomer predominates in solution, because it is more stable than the enol tautomer. Interconversion of the tautomers is called **keto–enol interconversion** or **tautomerization.**

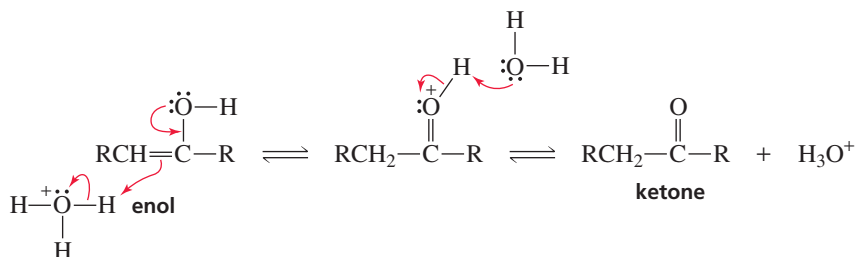
$$RCH{=}\overset{OH}{\overset{|}{C}}{-}R \rightleftharpoons RCH_2{-}\overset{O}{\overset{\|}{C}}{-}R$$

enol tautomer — keto tautomer

tautomerization

The mechanism for the conversion of an enol to a ketone under acidic conditions is shown next.

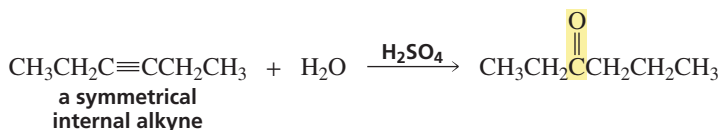
MECHANISM FOR ACID-CATALYZED KETO–ENOL INTERCONVERSION

$$RCH{=}\overset{:\ddot{O}-H}{\overset{|}{C}}{-}R \;\; (H{-}\overset{+}{\ddot{O}}(H){-}H) \rightleftharpoons RCH_2{-}\overset{H-\overset{+}{:O}}{\overset{\|}{C}}{-}R \;\; (:\ddot{O}H_2) \rightleftharpoons RCH_2{-}\overset{O}{\overset{\|}{C}}{-}R + H_3O^+$$

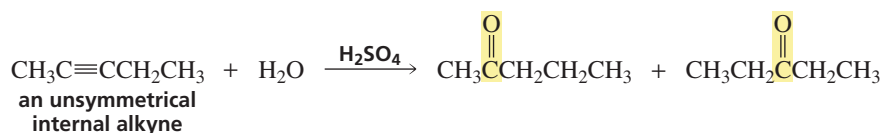
enol — ketone

- A π bond forms between carbon and oxygen and, as the π bond between the two carbons breaks, carbon picks up a proton.
- Water removes a proton from the protonated carbonyl group.

The addition of water to a symmetrical internal alkyne forms a single ketone as a product.

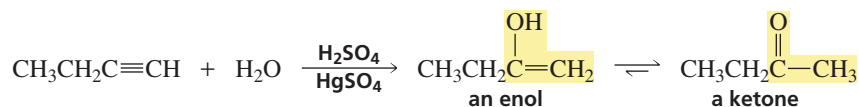
$$CH_3CH_2C{\equiv}CCH_2CH_3 + H_2O \xrightarrow{H_2SO_4} CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$$

a symmetrical internal alkyne

But if the alkyne is not symmetrical, two ketones are formed because the initial addition of the proton can occur to either of the *sp* carbons.

$$CH_3C{\equiv}CCH_2CH_3 + H_2O \xrightarrow{H_2SO_4} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 + CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$$

an unsymmetrical internal alkyne

Terminal alkynes are less reactive than internal alkynes toward the addition of water. The addition of water to a terminal alkyne will occur if mercuric ion (Hg^{2+}) is added to the acidic mixture. The mercuric ion is a catalyst—it increases the rate of the addition reaction.

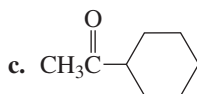
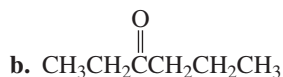
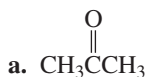
$$CH_3CH_2C{\equiv}CH + H_2O \xrightarrow[HgSO_4]{H_2SO_4} CH_3CH_2\overset{OH}{\overset{|}{C}}{=}CH_2 \rightleftharpoons CH_3CH_2\overset{O}{\overset{\|}{C}}{-}CH_3$$

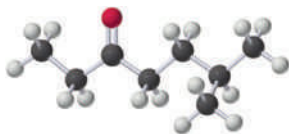
an enol — a ketone

PROBLEM 23♦

What ketones would be formed from the acid-catalyzed hydration of 3-heptyne?

PROBLEM 24♦

Which alkyne would be the best one to use for the synthesis of each of the following ketones?

a. $CH_3\overset{O}{\overset{\|}{C}}CH_3$ **b.** $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$ **c.** $CH_3\overset{O}{\overset{\|}{C}}{-}$cyclohexyl

PROBLEM 25♦

Draw the enol tautomers for the following ketone:

PROBLEM 26♦

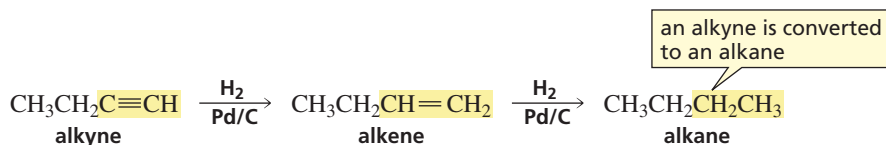
Draw all the enol tautomers for each of the ketones in Problem 24.

6.15 THE ADDITION OF HYDROGEN TO AN ALKYNE

Alkynes can be reduced by catalytic hydrogenation just as alkenes can (Section 5.6). The initial product of hydrogenation is an alkene, but it is difficult to stop the reaction at this stage because of hydrogen's strong tendency to add to alkenes in the presence of these efficient metal catalysts. The final product of the hydrogenation reaction, therefore, is an alkane.

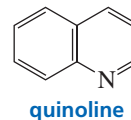
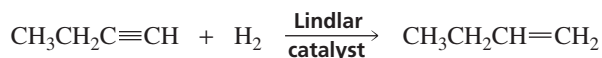
$$CH_3CH_2C{\equiv}CH \xrightarrow[Pd/C]{H_2} CH_3CH_2CH{=}CH_2 \xrightarrow[Pd/C]{H_2} CH_3CH_2CH_2CH_3$$

alkyne — alkene — alkane

an alkyne is converted to an alkane

The reaction can be stopped at the alkene stage if a "poisoned" (partially deactivated) metal catalyst is used. The most common partially deactivated metal catalyst is known as Lindlar catalyst (Figure 6.5).

$$CH_3CH_2C{\equiv}CH + H_2 \xrightarrow[\text{catalyst}]{\text{Lindlar}} CH_3CH_2CH{=}CH_2$$

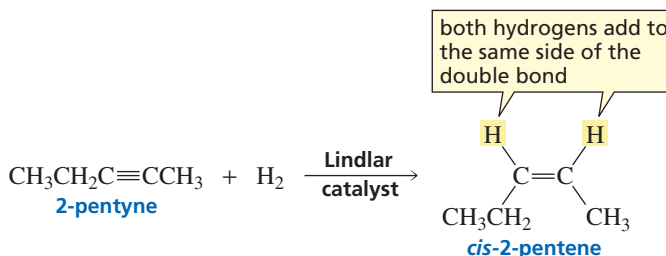
$(CH_3COO^-)_2Pb^{2+}$
lead(II) acetate

quinoline (structure)

▲ **Figure 6.5**
Lindlar catalyst is prepared by precipitating palladium on calcium carbonate and treating it with lead(II) acetate and quinoline. This treatment modifies the surface of palladium, making it much more effective at catalyzing the addition of hydrogen to a triple bond than to a double bond.

Because the alkyne sits on the surface of the metal catalyst and the hydrogens are delivered to the triple bond from the surface of the catalyst, both hydrogens are delivered to the same side of the double bond (Figure 5.3). Therefore, addition of hydrogen to an internal alkyne forms a *cis alkene*.

$$CH_3CH_2C{\equiv}CCH_3 + H_2 \xrightarrow[\text{catalyst}]{\text{Lindlar}} \text{cis-}CH_3CH_2(H)C{=}C(H)CH_3$$

2-pentyne → *cis*-2-pentene

both hydrogens add to the same side of the double bond

PROBLEM 27♦

Describe the alkyne you would start with and the reagents you would use to synthesize

a. pentane. **b.** *cis*-2-butene. **c.** 1-hexene.

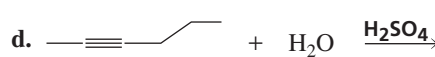
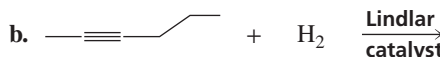
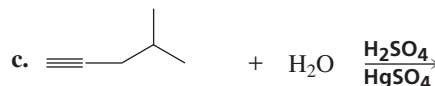
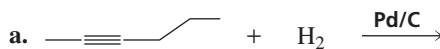
PROBLEM 28

What are products of the following reactions?

a. (alkyne) + H_2 $\xrightarrow{\text{Pd/C}}$

b. (alkyne) + H_2 $\xrightarrow[\text{catalyst}]{\text{Lindlar}}$

c. (alkyne) + H_2O $\xrightarrow[HgSO_4]{H_2SO_4}$

d. (alkyne) + H_2O $\xrightarrow{H_2SO_4}$

SOME IMPORTANT THINGS TO REMEMBER

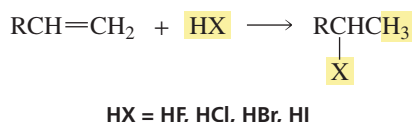
- **Alkenes** undergo **electrophilic addition reactions.** These reactions start with the addition of an *electrophile* to the *sp*^{2} carbon bonded to the most hydrogens and end with the addition of a nucleophile to the other *sp*^{2} carbon.
- A curved arrow always points from the electron donor to the electron acceptor.
- The addition of hydrogen halides and the acid-catalyzed addition of water and alcohols form **carbocation intermediates.**
- **Tertiary carbocations** are more stable than **secondary carbocations,** which are more stable than **primary carbocations.**
- The more stable carbocation is formed more rapidly.
- A carbocation can rearrange if the rearrangement results in a more stable carbocation.
- **Regioselectivity** is the preferential formation of one **constitutional isomer** over another.
- When a reactant that does not have an asymmetric center forms a product with an asymmetric center, the product will be a racemic mixture.
- An **alkyne** is a hydrocarbon that contains a carbon–carbon triple bond. The functional group suffix of an alkyne is "yne."
- When an enzyme catalyzes a reaction that forms a product with an asymmetric center, only one stereoisomer is formed.
- A **terminal alkyne** has the triple bond at the end of the chain; an **internal alkyne** has the triple bond located elsewhere along the chain.
- Alkynes undergo electrophilic addition reactions. The same reagents that add to alkenes also add to alkynes.
- If excess reagent is available, alkynes undergo a second addition reaction with hydrogen halides because the product of the first reaction is an alkene.
- The product of the reaction of an alkyne with water under acidic conditions is an **enol,** which immediately rearranges to a ketone. Terminal alkynes require a mercuric ion catalyst.
- The ketone and enol are called **keto–enol tautomers;** they differ in the location of a double bond and a hydrogen. The keto tautomer usually predominates at equilibrium.
- Interconversion of the tautomers is called **tautomerization** or **keto–enol interconversion.**
- Catalytic hydrogenation of an alkyne forms an alkane.
- Catalytic hydrogenation with Lindlar catalyst converts an internal alkyne to a *cis alkene*.

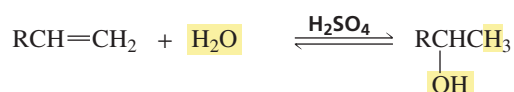
SUMMARY OF REACTIONS

As you review the electrophilic addition reactions of alkenes and alkynes, keep in mind that the first step in each of them is the addition of an electrophile to the sp^2 (or sp) carbon bonded to the most hydrogens.

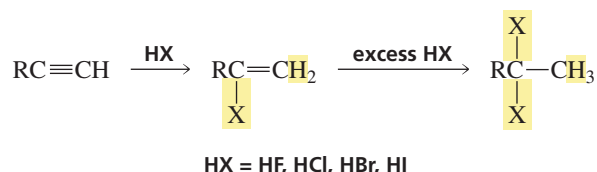
1. Addition of a hydrogen halide to an alkene: H^+ is the electrophile; the halide ion is the nucleophile (Sections 6.1 and 6.4). The mechanism is on page 212.

$$RCH{=}CH_2 + HX \longrightarrow RCH(X)CH_3$$

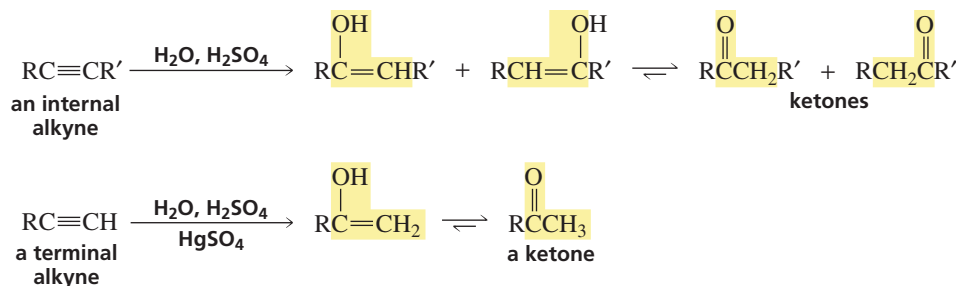
HX = HF, HCl, HBr, HI

2. Acid-catalyzed addition of water to an alkene: H^+ is the electrophile; water is the nucleophile (Section 6.5). The mechanism is on page 221.

$$RCH{=}CH_2 + H_2O \underset{}{\overset{H_2SO_4}{\rightleftharpoons}} RCH(OH)CH_3$$

3. Addition of a hydrogen halide to an alkyne: H^+ is the electrophile; the halide ion is the nucleophile (Section 6.13). The mechanism is on page 232.

$$RC{\equiv}CH \xrightarrow{HX} RC(X){=}CH_2 \xrightarrow{\text{excess HX}} RCX_2{-}CH_3$$

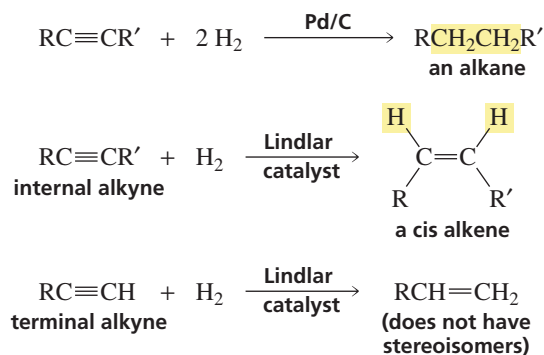
HX = HF, HCl, HBr, HI

4. Acid-catalyzed addition of water to an alkyne: H^+ is the electrophile; water is the nucleophile (Section 6.14). The mechanism for the acid-catalyzed conversion of an enol to a ketone is on page 234.

$$\underset{\text{an internal alkyne}}{RC{\equiv}CR'} \xrightarrow{H_2O,\ H_2SO_4} RC(OH){=}CHR' + RCH{=}C(OH)R' \rightleftharpoons \underset{\text{ketones}}{RC({=}O)CH_2R' + RCH_2C({=}O)R'}$$

$$\underset{\text{a terminal alkyne}}{RC{\equiv}CH} \xrightarrow[HgSO_4]{H_2O,\ H_2SO_4} RC(OH){=}CH_2 \rightleftharpoons \underset{\text{a ketone}}{RC({=}O)CH_3}$$

5. Addition of hydrogen to alkynes (Section 6.15).

$$RC{\equiv}CR' + 2\,H_2 \xrightarrow{Pd/C} \underset{\text{an alkane}}{RCH_2CH_2R'}$$

$$\underset{\text{internal alkyne}}{RC{\equiv}CR'} + H_2 \xrightarrow[\text{catalyst}]{\text{Lindlar}} \underset{\text{a cis alkene}}{(H)(R)C{=}C(H)(R')}$$

$$\underset{\text{terminal alkyne}}{RC{\equiv}CH} + H_2 \xrightarrow[\text{catalyst}]{\text{Lindlar}} \underset{\text{(does not have stereoisomers)}}{RCH{=}CH_2}$$

PROBLEMS

29. Identify the electrophile and the nucleophile in each of the following reaction steps, and then draw curved arrows to illustrate the bond-making and bond-breaking processes.

a. $CH_3\overset{+}{C}HCH_3 + :\ddot{Cl}:^- \longrightarrow CH_3CH(Cl)CH_3$ (with $:\ddot{Cl}:$ on the central carbon)

b. $CH_3CH{=}CH_2 + H{-}Br \longrightarrow CH_3\overset{+}{C}H{-}CH_3 + Br^-$

30. What is the major product of each of the following reactions?

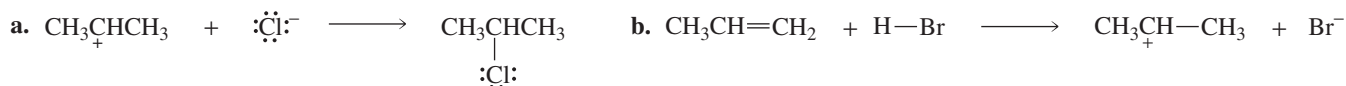
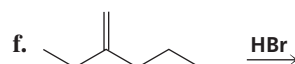
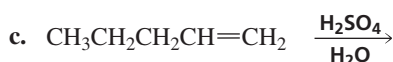
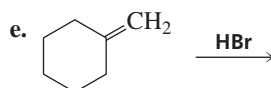
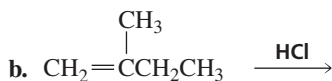
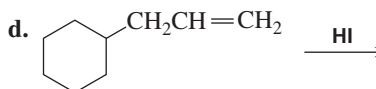
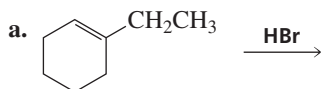
a. 1-ethylcyclohexene (CH_2CH_3 on the ring double bond) $\xrightarrow{HBr}$

b. $CH_2{=}C(CH_3)CH_2CH_3 \xrightarrow{HCl}$

c. $CH_3CH_2CH_2CH{=}CH_2 \xrightarrow[H_2O]{H_2SO_4}$

d. cyclohexyl–$CH_2CH{=}CH_2 \xrightarrow{HI}$

e. methylenecyclohexane (ring $={CH_2}$) $\xrightarrow{HBr}$

f. (skeletal alkene) $\xrightarrow{HBr}$

31. What will be the major product of the reaction of 3-methyl-2-pentene with each of the following reagents?

a. HBr **b.** HI **c.** H_2/Pd **d.** $H_2O + H_2SO_4$

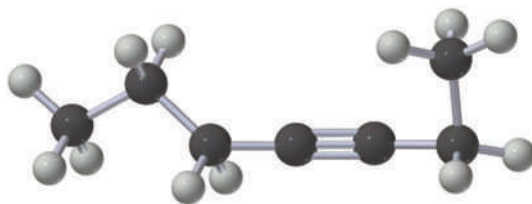
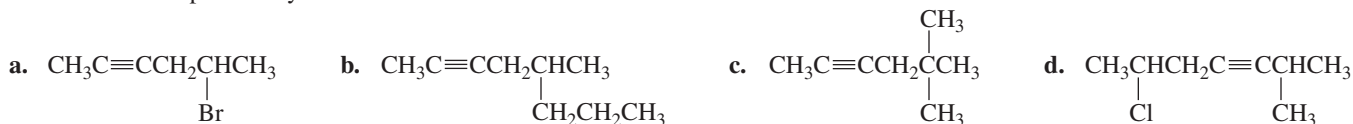
32. What ketones are formed when the following alkyne undergoes the acid-catalyzed addition of water?

33. What is each compound's systematic name?

a. $CH_3C{\equiv}CCH_2CH(Br)CH_3$

b. $CH_3C{\equiv}CCH_2CH(CH_2CH_2CH_3)CH_3$

c. $CH_3C{\equiv}CCH_2C(CH_3)_2CH_3$

d. $CH_3CH(Cl)CH_2C{\equiv}CCH(CH_3)CH_3$

34. What is the major product obtained from the reaction of each of the following compounds with excess HCl?

a. $CH_3CH_2C{\equiv}CH$ **b.** $CH_3CH_2C{\equiv}CCH_2CH_3$ **c.** $CH_3CH_2C{\equiv}CCH_2CH_2CH_3$

35. Draw a structure for each of the following:

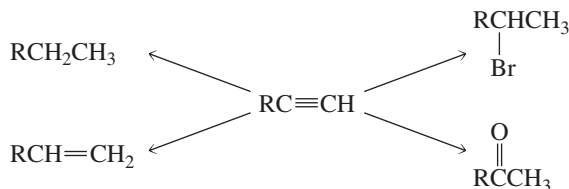
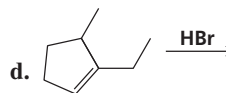
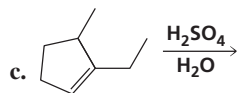
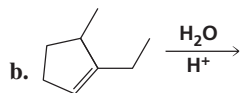
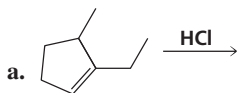
a. 3-hexyne **b.** 4-ethyl-2-octyne **c.** 3-bromo-1-pentyne **d.** 4,4-dimethyl-2-heptyne

36. What reagents could be used to carry out the following syntheses?

$RCH_2CH_3 \longleftarrow RC{\equiv}CH \longrightarrow RCH(Br)CH_3$

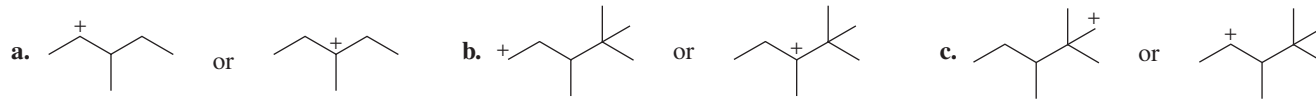
$RCH{=}CH_2 \longleftarrow RC{\equiv}CH \longrightarrow RC(=O)CH_3$

37. What is the major product of each of the following reactions?

a. (substituted cyclopentene) $\xrightarrow{HCl}$ **b.** (same) $\xrightarrow[H^+]{H_2O}$ **c.** (same) $\xrightarrow[H_2O]{H_2SO_4}$ **d.** (same) $\xrightarrow{HBr}$

38. Which is more stable?

a.

b.

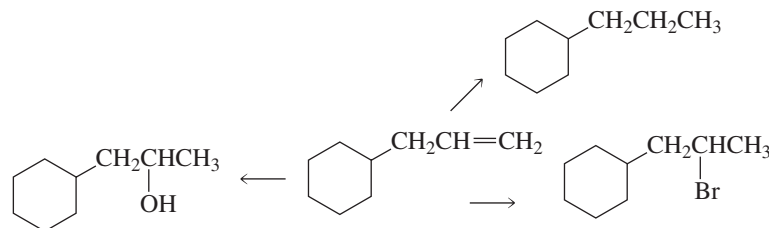
c.

39. A student was given the structural formulas of several compounds and was asked to give them systematic names. How many did she name correctly? Correct those that are misnamed.

a. 4-ethyl-2-pentyne **b.** 1-bromo-4-heptyne **c.** 2-methyl-3-hexyne **d.** 3-pentyne

40. Draw the structures and give the common and systematic names for alkynes with molecular formula C_7H_{12}. (*Hint:* There are 14.)

41. What reagents would be required to carry out the following syntheses?

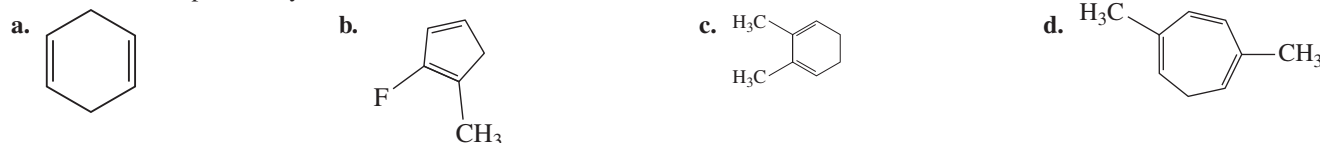
$CH_2CH_2CH_3$

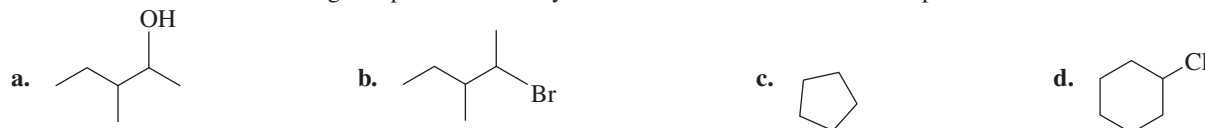
CH_2CHCH_3 (OH) ⟵ $CH_2CH{=}CH_2$ ⟶ CH_2CHCH_3 (Br)

42. What will be the major product of the reaction of 1 mol of propyne with each of the following reagents?

a. HBr (1 mol)
b. HBr (2 mol)
c. aqueous H_2SO_4, $HgSO_4$
d. excess H_2, Pd/C
e. H_2/Lindlar catalyst
f. $NaNH_2$

43. Answer Problem 42 using 2-butyne as the starting material instead of propyne.

44. What is each compound's systematic name?

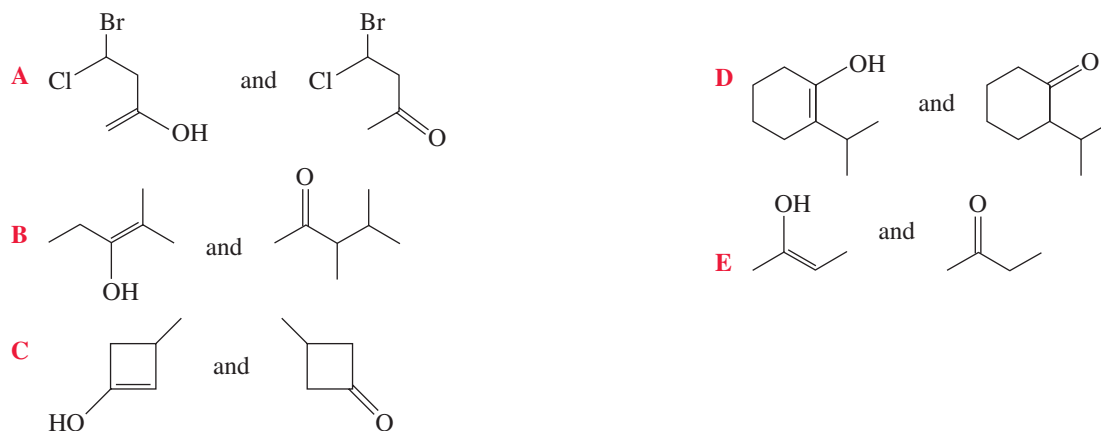
a. **b.** F, CH_3 **c.** H_3C, H_3C **d.** H_3C, CH_3

45. Show how each of the following compounds can be synthesized from an alkene in one step:

a. OH **b.** Br **c.** **d.** Cl

46. Draw the product or products that would be obtained from the reaction of *cis*-2-butene and *trans*-2-butene with each of the following reagents. If a product can exist as stereoisomers, show which stereoisomers are formed.

a. HCl **b.** $H_2 + Pd/C$ **c.** $H_2O + H_2SO_4$

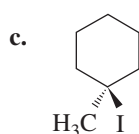
47. Which of the following pairs are keto–enol tautomers?

D OH and O

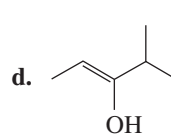
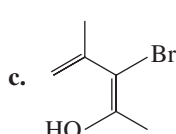
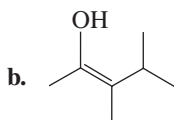
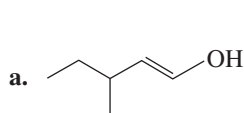
E OH and O

48. How many of the following names are correct? Correct those that are wrong.

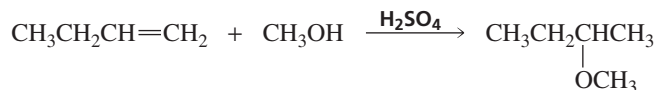
a. 4-heptyne
b. 2-ethyl-3-hexyne
c. 4-chloro-2-pentyne
d. 2,3-dimethyl-5-octyne
e. 4,4-dimethyl-2-pentyne
f. 2,5-dimethyl-3-hexyne

49. Using any alkene and any other reagents, how would you prepare the following compounds?

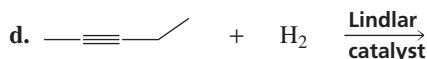
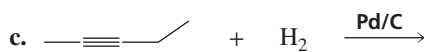
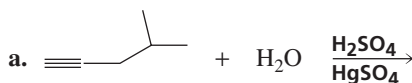
a. **b.** OH **c.** H_3C I

50. a. Identify two alkenes that react with HBr to form 1-bromo-1-methylcyclohexane.
b. Would both alkenes form the same alkyl halide if DBr were used instead of HBr? (D is an isotope of H, so D^+ reacts like H^+.)

51. Draw the keto tautomer for each of the following:

a.
b.
c.
d.

52. a. Propose a mechanism for the following reaction (show all curved arrows):

$$CH_3CH_2CH{=}CH_2 + CH_3OH \xrightarrow{H_2SO_4} CH_3CH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_3$$

b. Which step is the rate-determining step?
c. What is the electrophile in the first step?
d. What is the nucleophile in the first step?
e. What is the electrophile in the second step?
f. What is the nucleophile in the second step?

53. What are the products of the following reactions?

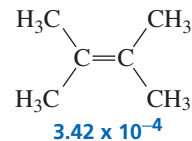
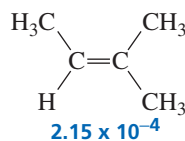
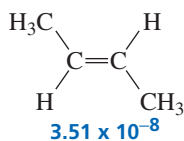
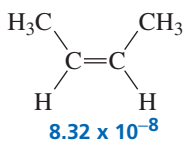
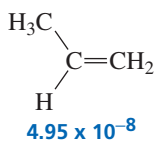
a. + H_2O $\xrightarrow[HgSO_4]{H_2SO_4}$
b. + H_2O $\xrightarrow{H_2SO_4}$
c. + H_2 $\xrightarrow{Pd/C}$
d. + H_2 $\xrightarrow[\text{catalyst}]{\text{Lindlar}}$

54. The second-order rate constant (in units of $M^{-1}s^{-1}$) for acid-catalyzed hydration at 25 °C is given for each of the following alkenes:

H_3C, H, C=CH_2 — 4.95×10^{-8}

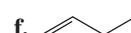
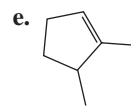
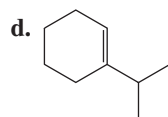
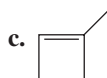
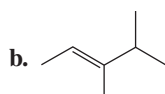
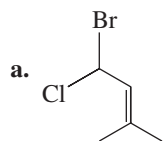
8.32×10^{-8}

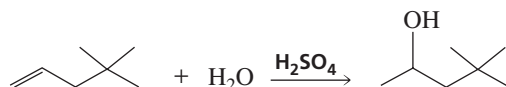
H_3C, H, C=C, H, CH_3 — 3.51×10^{-8}

H_3C, H, C=C, CH_3, CH_3 — 2.15×10^{-4}

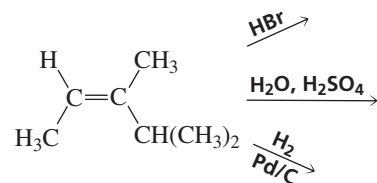
H_3C, H_3C, C=C, CH_3, CH_3 — 3.42×10^{-4}

a. Calculate the relative rates of hydration of the alkenes. (*Hint*: Divide each rate constant by the smallest rate constant of the series: 3.51×10^{-8}.)
b. Why does (*Z*)-2-butene react faster than (*E*)-2-butene?
c. Why does 2-methyl-2-butene react faster than (*Z*)-2-butene?
d. Why does 2,3-dimethyl-2-butene react faster than 2-methyl-2-butene?

55. What is the major product obtained from the reaction of HBr with each of the following?

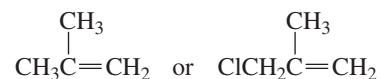
a. Br, Cl **b.** **c.** **d.** **e.** **f.**

56. Propose a mechanism for the following reaction:

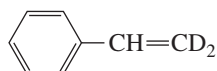
+ H_2O $\xrightarrow{H_2SO_4}$ OH

57. a. What product is obtained from the reaction of HCl with 1-butene? With 2-butene?
b. Which of the two reactions has the greater free energy of activation?
c. Which compound reacts more rapidly with HCl, (*Z*)-2-butene or (*E*)-2-butene?

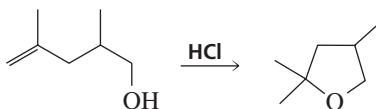
58. Draw the products of the following reactions, showing the stereoisomers that are formed:

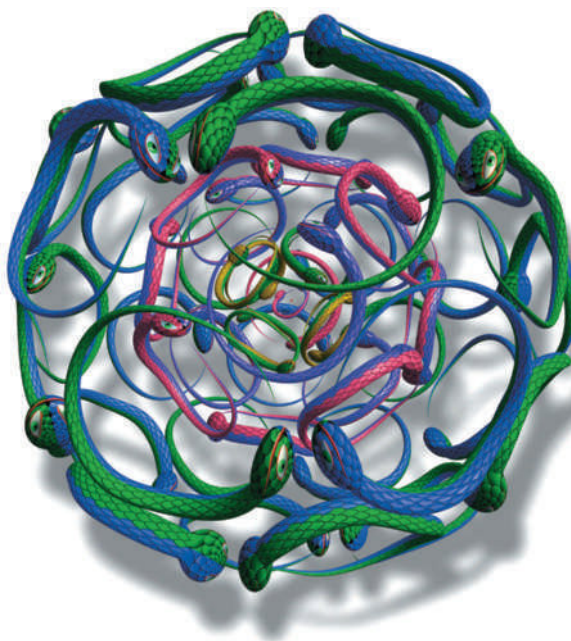
$$\begin{matrix} H & & CH_3 \\ & C{=}C & \\ H_3C & & CH(CH_3)_2 \end{matrix} \quad \begin{matrix} \xrightarrow{HBr} \\ \xrightarrow{H_2O,\ H_2SO_4} \\ \xrightarrow[Pd/C]{H_2} \end{matrix}$$

59. A student was about to turn in the products he had obtained from the reaction of HI with 3,3,3-trifluoropropene when he realized that the labels had fallen off his flasks and he did not know which label belonged to which flask. His friend reminded him of the rule that says the electrophile adds to the sp^2 carbon bonded to the most hydrogens. In other words, he should label the flask containing the most product 1,1,1-trifluoro-2-iodopropane and label the flask containing the least amount of product 1,1,1-trifluoro-3-iodopropane. Should he follow his friend's advice?

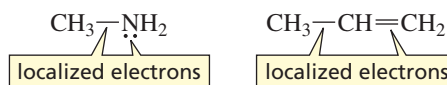
60. Which compound would you expect to be hydrated more rapidly?

$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2 \quad \text{or} \quad ClCH_2\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2$$

61. When the following compound is hydrated in the presence of acid, the unreacted alkene is found to have retained the deuterium atoms. What does this tell you about the mechanism for hydration?

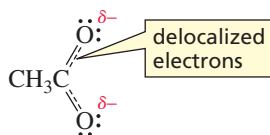
$$C_6H_5{-}CH{=}CD_2$$

62. Propose a reasonable mechanism for the following reaction:

$$\text{(alkenol)}\ \text{OH} \xrightarrow{HCl} \text{(cyclic ether)}\ \text{O}$$

7 Delocalized Electrons and Their Effect on Stability, pK_a, and the Products of a Reaction • Aromaticity and the Reactions of Benzene

Kekulé's Dream (see page 245)

Delocalized electrons play such an important role in organic chemistry that they will be a part of all the remaining chapters in this book. This chapter starts by showing you how delocalized electrons are depicted. Then you will see how they affect things that are now familiar to you, such as pK_a values, the stability of carbocations, and the products formed from electrophilic addition reactions.

Electrons that are restricted to a particular region are called **localized electrons.** Localized electrons either belong to a single atom or are shared by two atoms.

Many organic compounds have *delocalized* electrons. **Delocalized electrons** are shared by three or more atoms. You were first introduced to delocalized electrons in Section 2.8, where you saw that the two electrons represented by the π bond of the COO^- group are shared by three atoms—the carbon and both oxygens. The dashed lines in the chemical structure shown here indicate that the two electrons are delocalized over three atoms.

$$CH_3C(\overset{..}{\underset{}{O}}:^{\delta-})(\overset{..}{O}:^{\delta-})$$

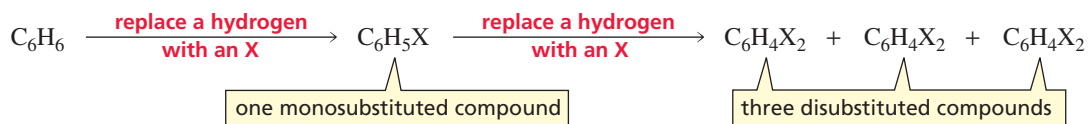
delocalized electrons

In this chapter, you will learn to recognize compounds that have delocalized electrons and how to draw structures that represent the electron distribution in molecules with delocalized electrons. You will also be introduced to some of the special characteristics of compounds that have delocalized electrons. You will then be able to understand some of the wide-ranging effects that delocalized electrons have on the reactions and properties of organic compounds. We begin by looking at benzene, a compound whose structure is ideal to illustrate the concept of delocalized electrons.

7.1 DELOCALIZED ELECTRONS EXPLAIN BENZENE'S STRUCTURE

Because early organic chemists did not know about delocalized electrons, they were puzzled by benzene's structure. They knew that benzene had a molecular formula of C_6H_6, that it was an unusually stable compound, and that it did not undergo the addition reactions characteristic of alkenes (Section 6.0). They also knew that when a different atom was substituted for any one of benzene's hydrogens, only *one* product was obtained and, when the substituted product underwent a second substitution, *three* products were obtained.

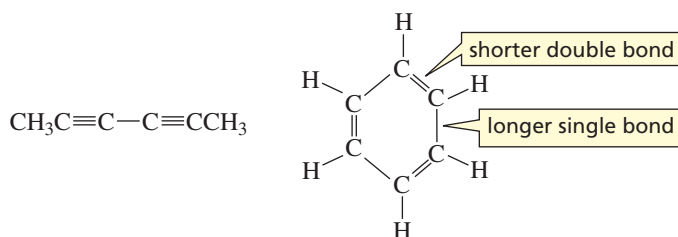
$$C_6H_6 \xrightarrow[\text{with an X}]{\text{replace a hydrogen}} C_6H_5X \xrightarrow[\text{with an X}]{\text{replace a hydrogen}} C_6H_4X_2 + C_6H_4X_2 + C_6H_4X_2$$

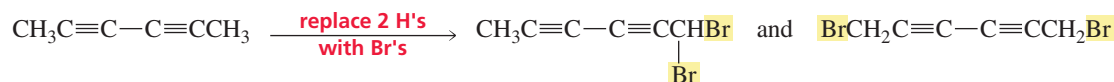
one monosubstituted compound

three disubstituted compounds

What kind of structure would you predict for benzene if you knew only what the early chemists knew? Because only one product is obtained regardless of which of the six hydrogens of benzene is replaced with another atom, we know that all the hydrogens must be identical. The molecular formula (C_6H_6) tells us that benzene has eight fewer hydrogens than an acyclic alkane with six carbons ($C_nH_{2n+2} = C_6H_{14}$). Each ring and π bond results in two fewer hydrogens than an acyclic alkane would have. Therefore, the total number of rings and π bonds in benzene is four. Two structures with a molecular formula of C_6H_6 and six identical hydrogens are shown here:

$$CH_3C{\equiv}C{-}C{\equiv}CCH_3$$

shorter double bond

longer single bond

Neither of these structures, however, is consistent with the observation that three compounds are obtained if a second hydrogen is replaced with another atom. The acyclic structure yields only two disubstituted products.

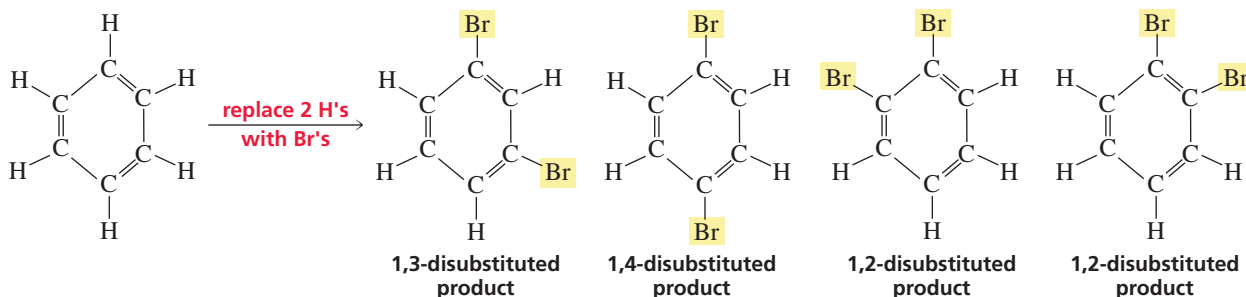
$$CH_3C{\equiv}C{-}C{\equiv}CCH_3 \xrightarrow[\text{with Br's}]{\text{replace 2 H's}} CH_3C{\equiv}C{-}C{\equiv}CCHBr_2 \quad \text{and} \quad BrCH_2C{\equiv}C{-}C{\equiv}CCH_2Br$$

The cyclic structure, with alternating single and slightly shorter double bonds, yields four disubstituted products—a 1,3-disubstituted product, a 1,4-disubstituted product, and two 1,2-disubstituted products—because the two substituents can be placed either on two adjacent carbons joined by a single bond or on two adjacent carbons joined by a double bond.

replace 2 H's with Br's

1,3-disubstituted product

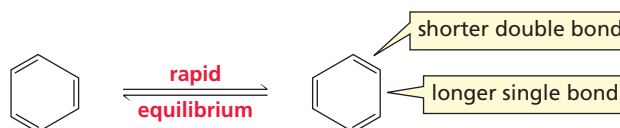
1,4-disubstituted product

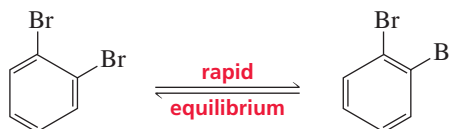
1,2-disubstituted product

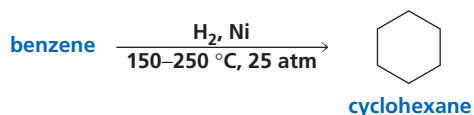
1,2-disubstituted product

In 1865, the German chemist Friedrich Kekulé suggested a way of resolving this dilemma. He proposed that benzene was not a single compound, but a mixture of two compounds in rapid equilibrium.

rapid equilibrium

shorter double bond

longer single bond

Kekulé's proposal explained why only three disubstituted products are obtained. According to Kekulé, there actually *are* four disubstituted products, but the two 1,2-disubstituted products interconvert too rapidly to be distinguished and separated from each other.

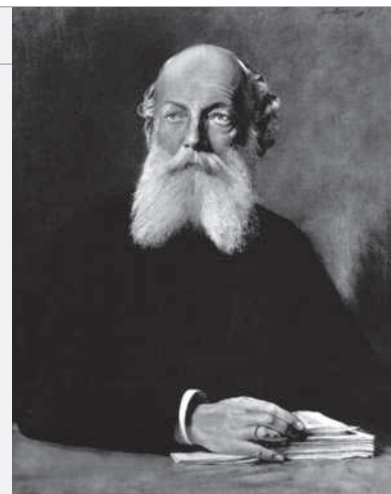
rapid equilibrium

In 1901, it was confirmed that benzene has a six-membered ring, when it was found that catalytic hydrogenation of benzene produced cyclohexane.

benzene $\xrightarrow[\text{150–250 °C, 25 atm}]{H_2, \text{ Ni}}$ cyclohexane

Controversy over the structure of benzene continued until the 1930s, when the new techniques of X-ray and electron diffraction produced a surprising result: they showed that *benzene is a planar molecule and that the six carbon–carbon bonds all have the same length*. The length of each carbon–carbon bond is 1.39 Å, which is shorter than a carbon–carbon single bond (1.54 Å) but longer than a carbon–carbon double bond (1.33 Å). In other words, benzene does not have alternating single and double bonds.

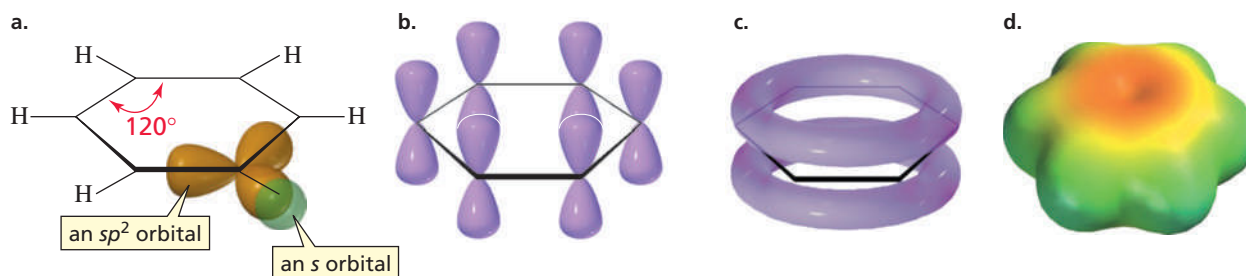
If the carbon–carbon bonds in benzene all have the same length, they must also have the same number of electrons between the carbons. This can be true, however, only if the π electrons are delocalized around the ring, rather than each pair of π electrons being localized between two carbons. To better understand the concept of delocalized electrons, we will now take a close look at the bonding in benzene.

Kekulé's Dream

Friedrich August Kekulé von Stradonitz (1829–1896) was born in Germany. He entered the University of Giessen to study architecture but switched to chemistry after taking a course in the subject. He was a professor of chemistry at the University of Heidelberg, at the University of Ghent in Belgium, and then at the University of Bonn. In 1890, he gave an extemporaneous speech at the twenty-fifth-anniversary celebration of his first paper on the cyclic structure of benzene. In this speech, he claimed that he had arrived at the structures as a result of dozing off in front of a fire while working on a textbook. He dreamed of chains of carbon atoms twisting and turning in a snakelike motion, when suddenly the head of one snake seized hold of its own tail and formed a spinning ring (see page 242).

Emperor William II of Germany made Kekulé a nobleman in 1895. This allowed him to add "von Stradonitz" to his name. Kekulé's students received three of the first five Nobel Prizes in Chemistry.

Friedrich August Kekulé von Stradonitz

7.2 THE BONDING IN BENZENE

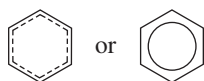
Each of benzene's six carbons is sp^2 hybridized. An sp^2 carbon has bond angles of 120°, which is identical to the size of the angles in a planar hexagon. Thus, benzene is a planar molecule (Figure 7.1a). Because benzene is planar, the six *p* orbitals are parallel (Figure 7.1b) and are close enough for each *p* orbital to overlap the *p* orbital on either side of it (Figure 7.1c).

▲ **Figure 7.1**

(a) Each of the carbons in benzene uses two sp^2 orbitals to bond to two other carbons; its third sp^2 orbital overlaps the *s* orbital of a hydrogen.

(b) Each carbon has a *p* orbital at right angles to the sp^2 orbitals. The parallel *p* orbitals are close enough for side-to-side overlap, so each *p* orbital overlaps the *p* orbitals on *both* adjacent carbons.

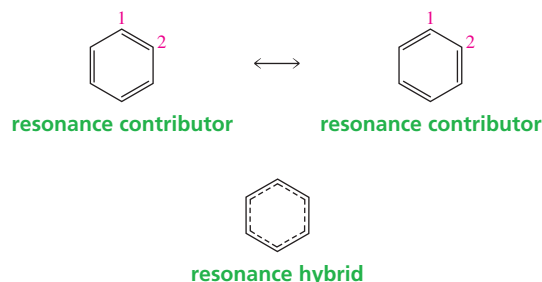
(c) The overlapping *p* orbitals form a continuous doughnut-shaped cloud of electrons above the plane of the benzene ring, and they form another doughnut-shaped cloud of electrons below it.

(d) The electrostatic potential map shows that all the carbon–carbon bonds have the same electron density.

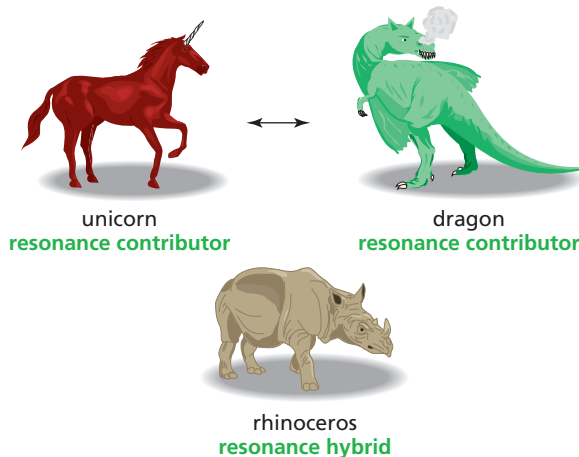
Each of the six π electrons of benzene, therefore, is localized neither on a single carbon nor in a bond between two carbons (as in an alkene). Instead, each π electron is shared by all six carbons. In other words, the six π electrons are delocalized—they roam freely within the doughnut-shaped clouds that lie over and under the planar ring of carbons (Figure 7.1c and d). Benzene is often drawn as a hexagon containing either dashed lines or a circle to symbolize the six delocalized π electrons.

This type of representation makes it clear that there are no double bonds in benzene. Kekulé's structure was very nearly correct. The actual structure of benzene is Kekulé's structure with delocalized electrons.

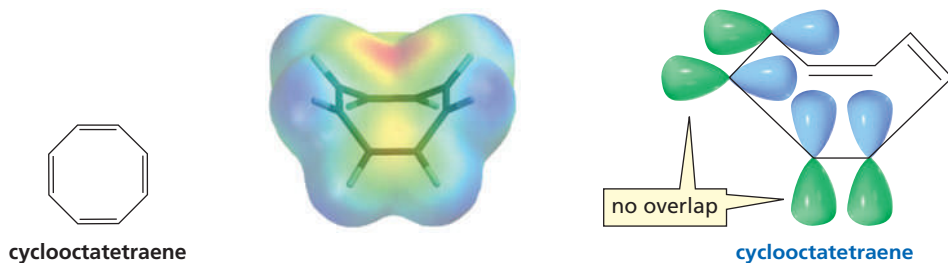
7.3 RESONANCE CONTRIBUTORS AND THE RESONANCE HYBRID

A disadvantage to using dashed lines (or a circle) to represent delocalized electrons is that they do not tell us how many π electrons they represent. For example, the dashed lines inside the hexagon just shown indicate that the π electrons are shared equally by all six carbons and that all the carbon–carbon bonds have the same length, but they do not show how many π electrons are in the ring. Consequently, chemists prefer to use structures that portray the electrons as localized (and therefore show the number of π electrons), even though the electrons in the compound's actual structure are delocalized.

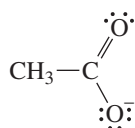
The *approximate* structure with localized electrons is called a **resonance contributor,** a **resonance structure,** or a **contributing resonance structure.** The *actual* structure with delocalized electrons is called a **resonance hybrid.** We can easily see that there are six π electrons in each of benzene's resonance contributors.

Electron delocalization is shown by double-headed arrows (⟷), whereas equilibrium is shown by two arrows pointing in opposite directions (⇌).

Resonance contributors are shown with a double-headed arrow between them. The double-headed arrow does *not* mean that the structures are in equilibrium with one another. Rather, it indicates that the actual structure lies somewhere *between* the structures of the resonance contributors. Resonance contributors are merely a convenient way to show the π electrons; they do not represent any real distribution of electrons.

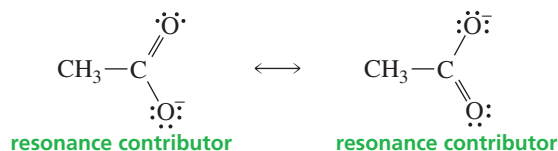
The following analogy illustrates the difference between resonance contributors and the resonance hybrid. Imagine that you are trying to describe to a friend what a rhinoceros looks like. You might tell your friend that a rhinoceros looks like a cross between a unicorn and a dragon. Like resonance contributors, the unicorn and the dragon do not really exist. Furthermore, like resonance contributors, they are not in equilibrium: a rhinoceros does not change back and forth between the two forms, looking like a unicorn one minute and a dragon the next. The unicorn and dragon are simply ways to describe what the actual animal—the rhinoceros—looks like. *Resonance contributors, like unicorns and dragons, are imaginary. Only the resonance hybrid, like the rhinoceros, is real.*

Electron delocalization is most effective if all the atoms sharing the delocalized electrons lie in the same plane, so that their *p* orbitals can maximally overlap.

For example, the electrostatic potential map shows that cyclooctatetraene is tub shaped, not planar—its sp^2 carbons have bond angles of 120°, whereas a planar eight-membered ring would have bond angles of 135°. Because the ring is not planar, a *p* orbital can overlap with one adjacent *p* orbital, but it can have little overlap with the other adjacent *p* orbital. As a result, the eight π electrons are localized in four double bonds and not delocalized over the entire eight-membered ring. Thus, the carbon–carbon bonds do not all have the same length.

7.4 HOW TO DRAW RESONANCE CONTRIBUTORS

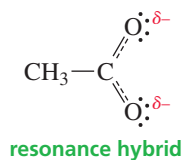
We have seen that an organic compound with delocalized electrons is generally represented as a structure with localized electrons to let us know how many π electrons it has. For example, the species shown here is usually represented with a carbon–oxygen double bond and a carbon–oxygen single bond.

$$CH_3-C(=\ddot{O})-\ddot{O}:^-$$

However, the two carbon–oxygen bonds actually have the same length. A more accurate description of the molecule's structure is obtained by drawing the two resonance contributors. Both resonance contributors show the compound with a carbon–oxygen double bond and a carbon–oxygen single bond; they indicate that the electrons are delocalized by depicting the double bond in one contributor as a single bond in the other.

$$CH_3-C(=\ddot{O})-\ddot{O}:^- \longleftrightarrow CH_3-C(-\ddot{O}:^-)=\ddot{O}$$

resonance contributor   resonance contributor

The resonance hybrid shows that the two π electrons are shared by three atoms. The resonance hybrid also shows that the two carbon–oxygen bonds are identical and that the negative charge is shared equally by both oxygens. Thus, we need to visualize and mentally average both resonance contributors to appreciate what the actual molecule—the resonance hybrid—looks like.

$$CH_3-C(\overset{..}{=}O:^{\delta-})(\overset{..}{=}O:^{\delta-})$$

resonance hybrid

Notice that *delocalized electrons result from a* p *orbital overlapping the* p *orbitals of two adjacent atoms*. For example, in the species shown here, the *p* orbital of carbon overlaps the *p* orbital of each of two adjacent oxygens, and in benzene, the *p* orbital of carbon overlaps the *p* orbital of each of two adjacent carbons.

Delocalized electrons result from a *p* orbital overlapping the *p* orbitals of two adjacent atoms.

Rules for Drawing Resonance Contributors

To draw a set of resonance contributors for a molecule, first draw a Lewis structure. This is the first resonance contributor. Then, following the rules listed next, move electrons to generate the next resonance contributor.

1. Only electrons move. Atoms never move.
2. Only π electrons (electrons in π bonds) and lone-pair electrons can be moved. (Never move σ electrons.)
3. The total number of electrons in the molecule does not change. Therefore, each of the resonance contributors for a particular compound must have the same net charge. If one has a net charge of 0, all the others must also have net charges of 0. (A net charge of 0 does not necessarily mean that there is no charge on any of the atoms, because a molecule with a positive charge on one atom and a negative charge on another atom has a net charge of 0.)

Notice, as you study the following resonance contributors and practice drawing them, that electrons (π electrons or lone pairs) are always moved toward an sp^2 atom. (Remember that an sp^2 carbon is either a positively charged carbon or a double-bonded carbon; Sections 1.8 and 1.10.) Electrons cannot be moved toward an sp^3 carbon because an sp^3 carbon has a complete octet and does not have a π bond that can break, so it cannot accommodate any more electrons.

The carbocation shown next has delocalized electrons. To draw its resonance contributor, *move the π electrons toward an* sp^2 *carbon*. By following the curved arrow, you can see how to draw the second contributor. Remember that the tail of the curved arrow shows where the electrons start from, and the head shows where the electrons end up. The resonance hybrid shows that the π electrons are shared by three carbons, and the positive charge is shared by two carbons.

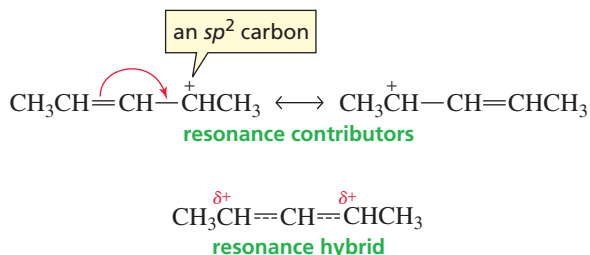
To draw resonance contributors, move only π electrons or lone pairs toward an *sp*^{2} carbon.

an sp^2 carbon

$$CH_3CH{=}CH{-}\overset{+}{C}HCH_3 \longleftrightarrow CH_3\overset{+}{C}H{-}CH{=}CHCH_3$$

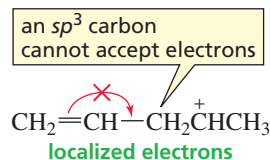
resonance contributors

$$CH_3\overset{\delta+}{C}H{\cdots}CH{\cdots}\overset{\delta+}{C}HCH_3$$

resonance hybrid

Let's compare this carbocation with a similar compound in which all the electrons are localized. The π electrons in the carbocation shown next cannot move, because the carbon they would move toward is an sp^3 carbon, and sp^3 carbons cannot accept any more electrons.

an sp^3 carbon cannot accept electrons

$$CH_2{=}CH{-}CH_2\overset{+}{C}HCH_3$$

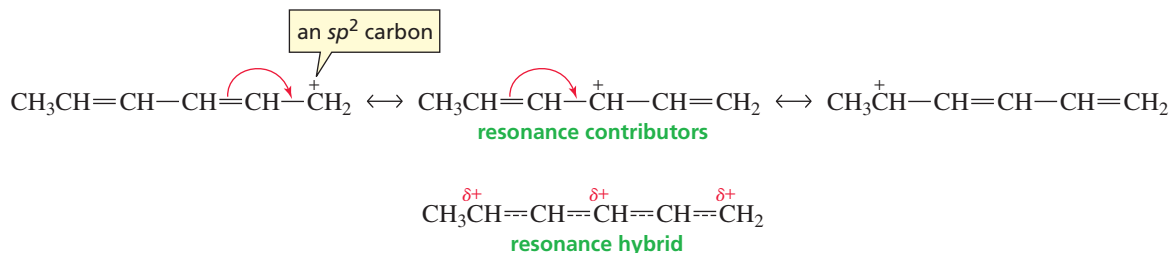
localized electrons

In the next example, *π electrons again move toward an* sp^2 *carbon*. The resonance hybrid shows that the π electrons are shared by five carbons, and positive charge is shared by three carbons.

an sp^2 carbon

$$CH_3CH{=}CH{-}CH{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow CH_3CH{=}CH{-}\overset{+}{C}H{-}CH{=}CH_2 \longleftrightarrow CH_3\overset{+}{C}H{-}CH{=}CH{-}CH{=}CH_2$$

resonance contributors

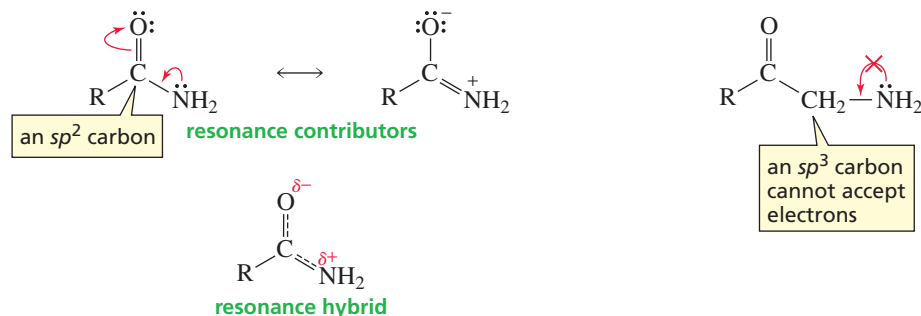
$$CH_3\overset{\delta+}{C}H{\cdots}CH{\cdots}\overset{\delta+}{C}H{\cdots}CH{\cdots}\overset{\delta+}{C}H_2$$

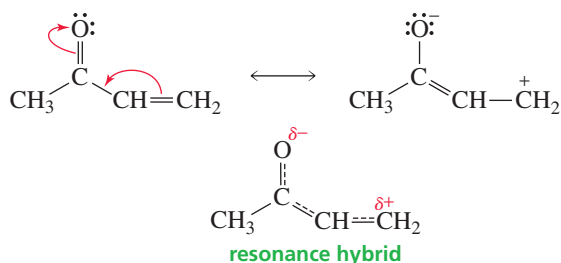
resonance hybrid

The resonance contributor for the next compound is obtained by *moving lone-pair electrons toward an* sp^2 *carbon*. The sp^2 carbon can accommodate the new electrons by breaking a π bond. The lone-pair electrons in the compound on the far right are not delocalized because they would have to move toward an sp^3 carbon.

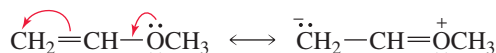
an sp^2 carbon

resonance contributors

resonance hybrid

an sp^3 carbon cannot accept electrons

The following resonance contributors are obtained by *moving* π *electrons toward an* sp^2 *carbon*. Notice that the electrons move toward (not away from) the most electronegative atom (the oxygen).

resonance hybrid

The only time you move electrons away from the most electronegative atom is when that is the only way electrons can be moved in order to arrive at a resonance contributor. In other words, movement of electrons away from the most electronegative atom is better than no movement at all, because electron delocalization makes a molecule more stable (as you will see in Section 7.6).

$$CH_2{=}CH{-}\ddot{O}CH_3 \longleftrightarrow \overset{-}{C}H_2{-}CH{=}\overset{+}{O}CH_3$$

PROBLEM 1

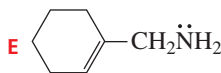
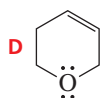
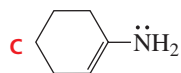
a. Which of the following compounds have delocalized electrons?

A $CH_3CH{=}CHCH{=}CH\overset{+}{C}H_2$

B $CH_3CH_2\ddot{N}HCH_2CH{=}CH_2$

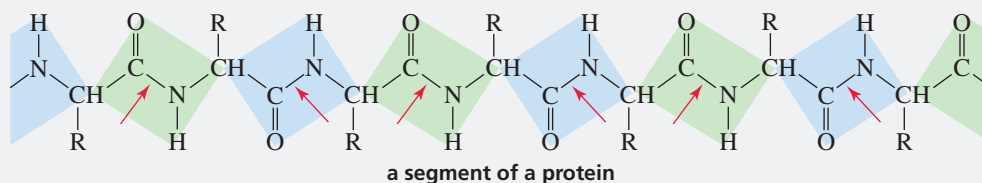
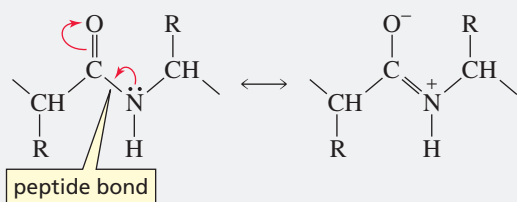
C (cyclohexenyl)$-\ddot{N}H_2$

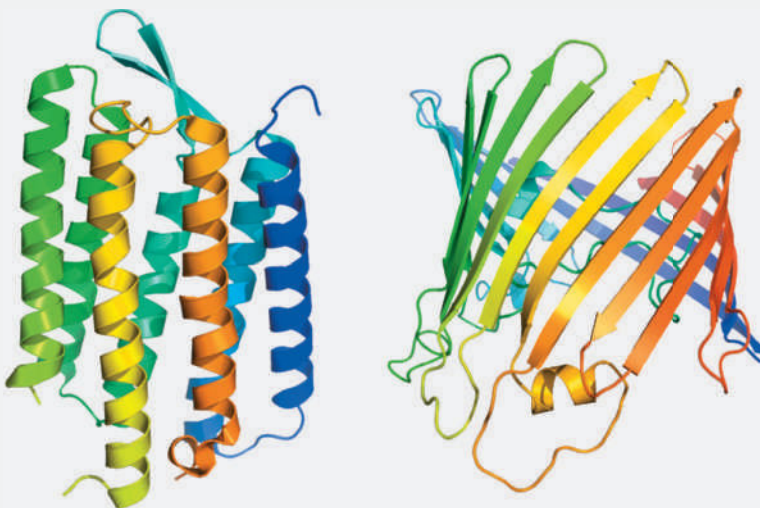
D (dihydropyran ring with $\ddot{O}$)

E (cyclohexenyl)$-CH_2\ddot{N}H_2$

b. Draw the resonance contributors for the compounds that have delocalized electrons.

Electron Delocalization Affects the Three-Dimensional Shape of Proteins

A protein consists of amino acids joined together by peptide bonds. Every third bond in a protein is a peptide bond, as indicated by the red arrows.

a segment of a protein

A resonance contributor can be drawn for a peptide bond by moving the lone pair on nitrogen toward the sp^2 carbon.

peptide bond

Because of the partial double-bond character of the peptide bond, the carbon and nitrogen atoms and the two atoms bonded to each of them are held rigidly in a plane, as represented in the protein segment by the blue and green boxes. Despite the rigid orientation of the peptide bond, the single bonds in the protein chain are free to rotate. Because of this, the chain is free to fold into a myriad of complex and highly intricate shapes. (Two conceptual representations of proteins are shown here; see also Figure 17.10 on page 601.)

7.5 THE PREDICTED STABILITIES OF RESONANCE CONTRIBUTORS

All resonance contributors do not necessarily contribute equally to the resonance hybrid. The degree to which each one contributes depends on its predicted stability. Because resonance contributors are not real, their stabilities cannot be measured. Therefore, the stabilities of resonance contributors have to be predicted based on molecular features found in real molecules.

The greater the predicted stability of a resonance contributor, the more it contributes to the structure of the resonance hybrid.

The more the resonance contributor contributes to the structure of the resonance hybrid, the more similar the contributor is to the real molecule.

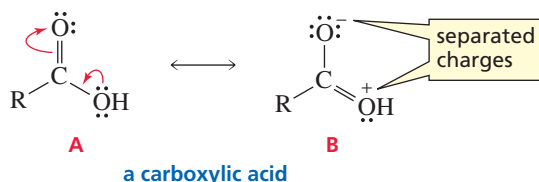
The examples that follow illustrate these points.

The two resonance contributors for a carboxylic acid have different predicted stabilities. **B** has two features that make it less stable than **A:** one of the oxygens has a positive charge—not a stable situation for an electronegative atom—and the structure has separated charges. A molecule with **separated charges** has a positive charge and a negative charge that can be neutralized by the movement of electrons. Resonance contributors with separated charges are relatively unstable (relatively high in energy) because energy is required to keep the opposite charges separated. **A,** therefore, is predicted to be more

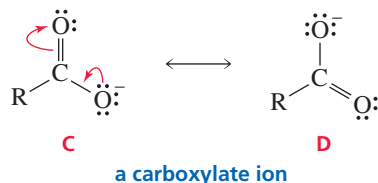
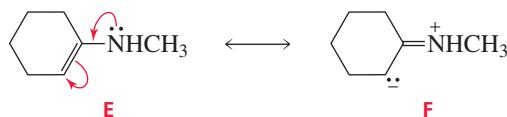
stable than **B.** Consequently, **A** makes a greater contribution to the resonance hybrid, so the resonance hybrid looks more like **A** than like **B.**

separated charges

A B

a carboxylic acid

The two resonance contributors for a carboxylate ion are shown next. **C** and **D** are equally stable, so they contribute equally to the resonance hybrid.

C D

a carboxylate ion

E is predicted to be more stable than **F,** because **F** has separated charges and its nitrogen has a positive charge. Therefore, the resonance hybrid is more similar to **E,** with only a small contribution from **F.**

$NHCH_3$ ⟷ $\overset{+}{N}HCH_3$

E F

The greater the predicted stability of a resonance contributor, the more it contributes to the structure of the resonance hybrid.

The more the resonance contributor contributes to the structure of the hybrid, the more similar that contributor is to the real molecule.

One of the next resonance contributors has a negative charge on carbon and the other has a negative charge on oxygen. Oxygen can better accommodate the negative charge (because it is more electronegative than carbon), so **H** is predicted to be more stable than **G**.

G H

PROBLEM 2 Solved

Draw resonance contributors for each of the following species and rank them in order of decreasing contribution to the hybrid:

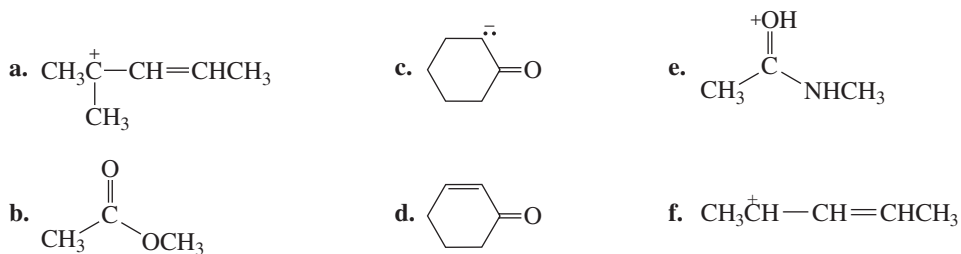
a. $CH_3\overset{+}{C}-CH=CHCH_3$ (with CH_3 on the charged carbon)

b. $CH_3C(=O)OCH_3$

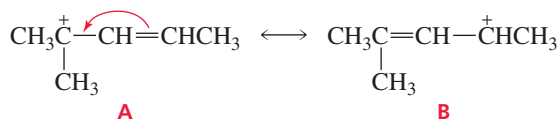
c. (cyclohexanone carbanion)

d. (cyclohexenone)

e. $CH_3C(=\overset{+}{O}H)NHCH_3$

f. $CH_3\overset{+}{C}H-CH=CHCH_3$

Solution to 2a **A** is more stable than **B** because the positive charge is on a tertiary carbon in **A,** whereas it is on a secondary carbon in **B,** and a tertiary carbocation is more stable than a secondary carbocation (Section 6.2).

$CH_3\overset{+}{C}(CH_3)-CH=CHCH_3 \longleftrightarrow CH_3C(CH_3)=CH-\overset{+}{C}HCH_3$

A B

PROBLEM 3

Draw the resonance hybrid for each of the species in Problem 2.

7.6 DELOCALIZATION ENERGY IS THE ADDITIONAL STABILITY DELOCALIZED ELECTRONS GIVE TO A COMPOUND

Delocalized electrons stabilize a compound. The extra stability a compound gains from having delocalized electrons is called the **delocalization energy. Electron delocalization** is also called **resonance,** so delocalization energy is also called **resonance energy.** Because delocalized electrons increase the stability of a compound, we can conclude that *a resonance hybrid is more stable than any of its resonance contributors is predicted to be*.

The delocalization energy associated with a compound that has delocalized electrons depends on the number *and* the predicted stability of the resonance contributors.

The delocalization energy is a measure of how much more stable a compound with delocalized electrons is than it would be if its electrons were localized.

The greater the number of relatively stable resonance contributors, the greater is the delocalization energy.

For example, the delocalization energy of a carboxylate ion with two relatively stable resonance contributors is significantly greater than the delocalization energy of a carboxylic acid with only one relatively stable resonance contributor.

The greater the number of relatively stable resonance contributors, the greater the delocalization energy.

$RC(=O)OH \longleftrightarrow RC(O^-)=\overset{+}{O}H$

relatively stable — relatively unstable

resonance contributors of a carboxylic acid

$RC(=O)O^- \longleftrightarrow RC(O^-)=O$

relatively stable — relatively stable

resonance contributors of a carboxylate ion

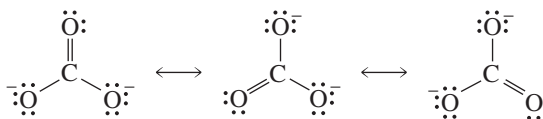
Notice that it is the number of *relatively stable* resonance contributors—not the total number of resonance contributors—that is important in determining the delocalization energy.

For example, the delocalization energy of a carboxylate ion with two relatively stable resonance contributors is greater than the delocalization energy of the following compound with three resonance contributors since only one of its resonance contributors is relatively stable:

$\overset{-}{C}H_2-CH=CH-\overset{+}{C}H_2 \longleftrightarrow CH_2=CH-CH=CH_2 \longleftrightarrow \overset{+}{C}H_2-CH=CH-\overset{-}{C}H_2$

relatively unstable — relatively stable — relatively unstable

The more nearly equivalent the structures of the resonance contributors, the greater the delocalization energy.

For example, the carbonate dianion is particularly stable because it has three equivalent resonance contributors.

The more nearly equivalent the structures of the resonance contributors, the greater the delocalization energy.

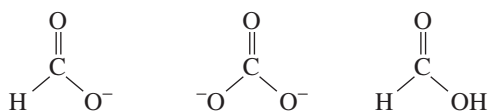
$O=C(O^-)O^- \longleftrightarrow {}^-O-C(=O)-O^- \longleftrightarrow {}^-O-C(O^-)=O$

PROBLEM 4♦

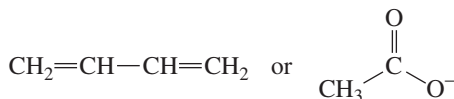
a. Predict the relative bond lengths of the three carbon–oxygen bonds in the carbonate ion (CO_3^{2-}).

b. What would you expect the charge to be on each oxygen?

PROBLEM 5♦

Rank the following species in order of decreasing delocalization energy:

PROBLEM 6♦

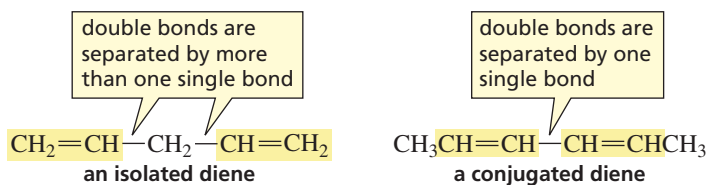
Which species has the greater delocalization energy?

$CH_2{=}CH{-}CH{=}CH_2$ or CH_3COO^-

7.7 DELOCALIZED ELECTRONS INCREASE STABILITY

We will now look at some examples that illustrate the extra stability a molecule acquires as a result of having delocalized electrons.

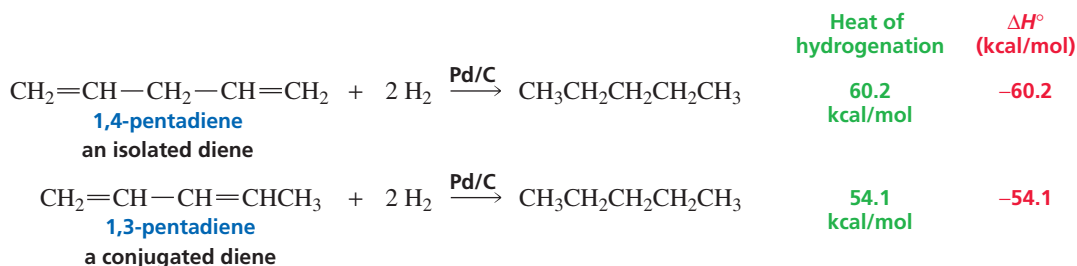
Stability of Dienes

Dienes are hydrocarbons with two double bonds.

- **Isolated dienes** have isolated double bonds; **isolated double bonds** are separated by more than one single bond.
- **Conjugated dienes** have conjugated double bonds; **conjugated double bonds** are separated by one single bond.

We saw in Section 5.6 that the relative stabilities of alkenes can be determined by their heats of hydrogenation. Recall that the most stable alkene has the smallest heat of hydrogenation; it gives off the least heat when it is hydrogenated because it has less energy to begin with.

The heat of hydrogenation of 1,3-pentadiene (a conjugated diene) is smaller than that of 1,4-pentadiene (an isolated diene). *A conjugated diene, therefore, is more stable than an isolated diene.*

The most stable alkene has the smallest heat of hydrogenation.

Reaction	Heat of hydrogenation	ΔH° (kcal/mol)
$CH_2{=}CH{-}CH_2{-}CH{=}CH_2 + 2\,H_2 \xrightarrow{Pd/C} CH_3CH_2CH_2CH_2CH_3$ **1,4-pentadiene** **an isolated diene**	60.2 kcal/mol	−60.2
$CH_2{=}CH{-}CH{=}CHCH_3 + 2\,H_2 \xrightarrow{Pd/C} CH_3CH_2CH_2CH_2CH_3$ **1,3-pentadiene** **a conjugated diene**	54.1 kcal/mol	−54.1

Why is a conjugated diene more stable than an isolated diene? The π electrons in each of the double bonds of an isolated diene are *localized* between two carbons. In contrast,

An increase in delocalization energy means an increase in stability.

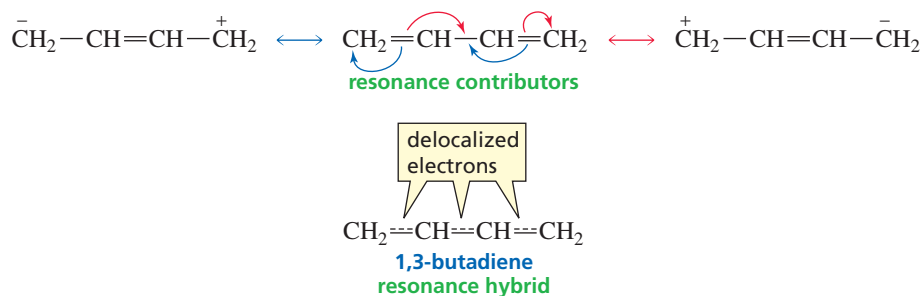
the π electrons in a conjugated diene are *delocalized*, and electron delocalization stabilizes a compound.

$$\overset{-}{C}H_2-CH=CH-\overset{+}{C}H_2 \longleftrightarrow CH_2=CH-CH=CH_2 \longleftrightarrow \overset{+}{C}H_2-CH=CH-\overset{-}{C}H_2$$

resonance contributors

delocalized electrons

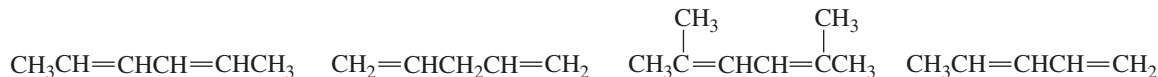
$$CH_2 \overset{...}{=} CH \overset{...}{=} CH \overset{...}{=} CH_2$$

1,3-butadiene
resonance hybrid

PROBLEM 7♦

Which is more stable, 2,4-heptadiene or 2,5-heptadiene?

PROBLEM 8♦

Name the following dienes and rank them in order from most stable to least stable. (Alkyl groups stabilize dienes in the same way that they stabilize alkenes; Section 5.6.)

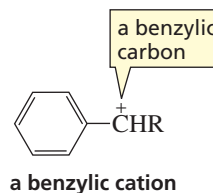
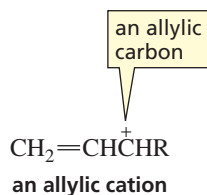
$CH_3CH=CHCH=CHCH_3$ $\quad$ $CH_2=CHCH_2CH=CH_2$ $\quad$ $CH_3\underset{}{\overset{CH_3}{C}}=CHCH=\overset{CH_3}{C}CH_3$ $\quad$ $CH_3CH=CHCH=CH_2$

Stability of Allylic and Benzylic Cations

Now we will look at carbocations that have delocalized electrons and are therefore more stable than similar carbocations with localized electrons.

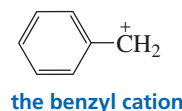
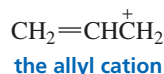
- An **allylic cation** is a carbocation with a positive charge on an allylic carbon; an **allylic carbon** is a carbon adjacent to an sp^2 carbon of an alkene (Section 5.1).
- A **benzylic cation** is a carbocation with a positive charge on a benzylic carbon; a **benzylic carbon** is a carbon adjacent to an sp^2 carbon of a benzene ring.

allyl cation

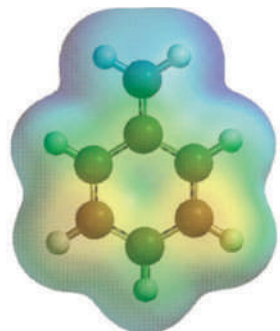
$CH_2=CH\overset{+}{C}HR$
an allylic cation

$C_6H_5-\overset{+}{C}HR$
a benzylic cation

The *allyl cation* is an unsubstituted allylic cation, and the *benzyl cation* is an unsubstituted benzylic cation.

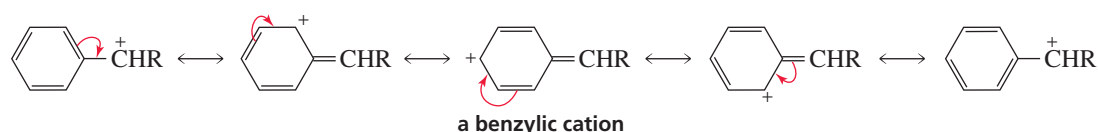
$CH_2=CH\overset{+}{C}H_2$
the allyl cation

$C_6H_5-\overset{+}{C}H_2$
the benzyl cation

benzyl cation

An allylic cation has two resonance contributors. The positive charge is not localized on a single carbon but is shared by two carbons.

$$RCH=CH-\overset{+}{C}H_2 \longleftrightarrow R\overset{+}{C}H-CH=CH_2$$

an allylic cation

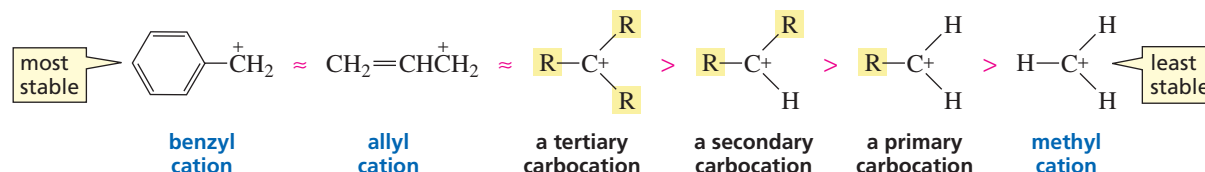
A benzylic cation has five resonance contributors. Notice that the positive charge is shared by four carbons.

$$C_6H_5\overset{+}{C}HR \longleftrightarrow \; =CHR \longleftrightarrow \; =CHR \longleftrightarrow \; =CHR \longleftrightarrow C_6H_5\overset{+}{C}HR$$

a benzylic cation

Because the allyl and benzyl cations have delocalized electrons, they are more stable than other primary carbocations in solution. We can add them to the list of carbocations whose relative stabilities were shown in Section 6.2.

relative stabilities of carbocations

most stable → $C_6H_5\overset{+}{C}H_2 \approx CH_2{=}CH\overset{+}{C}H_2 \approx R{-}\overset{+}{C}R_2 > R{-}\overset{+}{C}(R)H > R{-}\overset{+}{C}H_2 > H{-}\overset{+}{C}H_2$ ← least stable

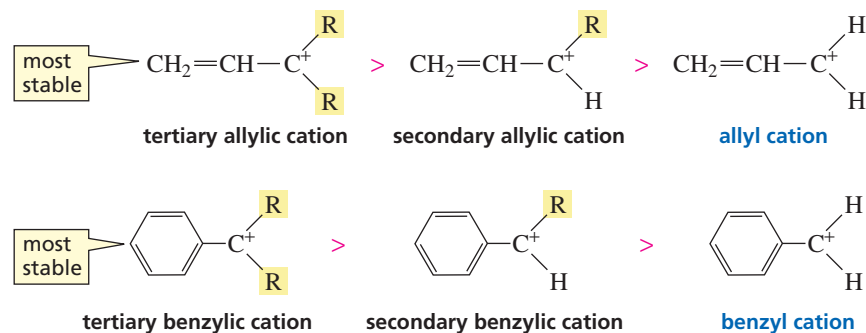
benzyl cation; allyl cation; a tertiary carbocation; a secondary carbocation; a primary carbocation; methyl cation

Not all allylic and benzylic cations have the same stability. Just as a tertiary alkyl carbocation is more stable than a secondary alkyl carbocation, a tertiary allylic cation is more stable than a secondary allylic cation, which in turn is more stable than the (primary) allyl cation. Similarly, a tertiary benzylic cation is more stable than a secondary benzylic cation, which is more stable than the (primary) benzyl cation.

relative stabilities

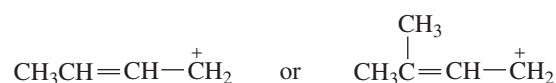
most stable → $CH_2{=}CH{-}\overset{+}{C}R_2 > CH_2{=}CH{-}\overset{+}{C}(R)H > CH_2{=}CH{-}\overset{+}{C}H_2$

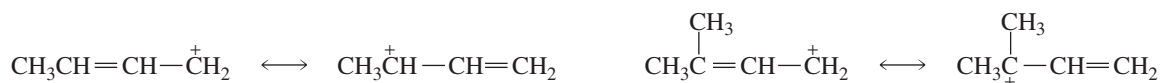
tertiary allylic cation; secondary allylic cation; allyl cation

most stable → $C_6H_5{-}\overset{+}{C}R_2 > C_6H_5{-}\overset{+}{C}(R)H > C_6H_5{-}\overset{+}{C}H_2$

tertiary benzylic cation; secondary benzylic cation; benzyl cation

PROBLEM-SOLVING STRATEGY

Which carbocation is more stable?

$$CH_3CH{=}CH{-}\overset{+}{C}H_2 \quad \text{or} \quad CH_3\underset{}{C}(CH_3){=}CH{-}\overset{+}{C}H_2$$

Start by drawing the resonance contributors for each carbocation. Then compare their predicted stabilities.

$$CH_3CH{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow CH_3\overset{+}{C}H{-}CH{=}CH_2 \qquad CH_3C(CH_3){=}CH{-}\overset{+}{C}H_2 \longleftrightarrow CH_3\underset{+}{C}(CH_3){-}CH{=}CH_2$$

Each carbocation has two resonance contributors. The positive charge of the carbocation on the left is shared by a primary allylic carbon and a secondary allylic carbon. The positive charge of the carbocation on the right is shared by a primary allylic carbon and a tertiary allylic carbon. Because a tertiary allylic carbon is more stable than a secondary allylic carbon, the carbocation on the right is more stable.

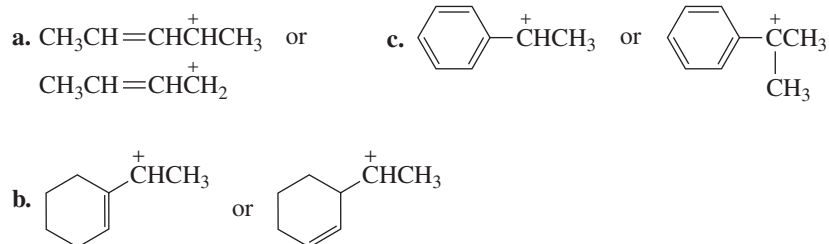
Now continue on to Problem 9.

PROBLEM 9♦

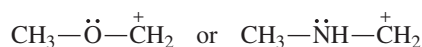
Which carbocation in each of the following pairs is more stable?

a. $CH_3CH{=}CH\overset{+}{C}HCH_3$ or $CH_3CH{=}CH\overset{+}{C}H_2$

b. (cyclohexenyl)$-\overset{+}{C}HCH_3$ or (cyclohexenyl)$-\overset{+}{C}HCH_3$

c. $C_6H_5-\overset{+}{C}HCH_3$ or $C_6H_5-\overset{+}{C}(CH_3)CH_3$

PROBLEM-SOLVING STRATEGY

Which species is more stable?

$$CH_3-\ddot{\underset{..}{O}}-\overset{+}{C}H_2 \quad \text{or} \quad CH_3-\ddot{N}H-\overset{+}{C}H_2$$

Start by drawing the resonance contributors for each species. Then compare their predicted stabilities.

$$CH_3-\ddot{\underset{..}{O}}-\overset{+}{C}H_2 \longleftrightarrow CH_3-\overset{+}{\underset{..}{O}}{=}CH_2 \qquad CH_3-\ddot{N}H-\overset{+}{C}H_2 \longleftrightarrow CH_3-\overset{+}{N}H{=}CH_2$$

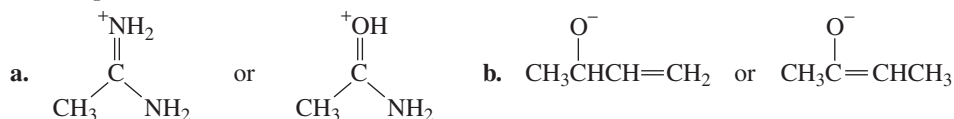
Each species has two resonance contributors. The positive charge of the species on the left is shared by an oxygen and a carbon. The positive charge of the species on the right is shared by a nitrogen and a carbon. Because nitrogen is less electronegative than oxygen, the predicted stability of the resonance contributor with a positive charge on nitrogen is greater than the predicted stability of the resonance contributor with a positive charge on oxygen. Therefore, the species on the right (with a more stable resonance contributor) is more stable.

Now continue on to Problem 10.

PROBLEM 10♦

Which species is more stable?

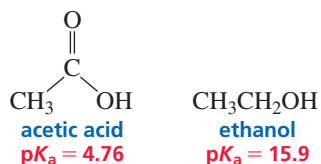
a. $CH_3C(={}^{+}NH_2)NH_2$ or $CH_3C(={}^{+}OH)NH_2$

b. $CH_3\overset{O^-}{\overset{|}{C}}HCH{=}CH_2$ or $CH_3\overset{O^-}{\overset{|}{C}}{=}CHCH_3$

7.8 DELOCALIZED ELECTRONS AFFECT pK_a VALUES

We saw in Section 2.7 that a carboxylic acid is a stronger acid than an alcohol, because the carboxylate ion (the conjugate base of the carboxylic acid) is a more stable (weaker) base than the alkoxide ion (the conjugate base of an alcohol). Recall that the more stable the base, the stronger its conjugate acid.

A nearby electronegative atom stabilizes an anion by inductive electron withdrawal.

$CH_3C(=O)OH$ — acetic acid, pK_a = 4.76

CH_3CH_2OH — ethanol, pK_a = 15.9

We also saw that the greater stability of the carboxylate ion is attributable to two factors—inductive electron withdrawal and electron delocalization. That is, the double-bonded

oxygen stabilizes the carboxylate ion by decreasing the electron density of the negatively charged oxygen by inductive *electron withdrawal*. The carboxylate ion is also stabilized by *electron delocalization*.

acetic acid

acetate ion

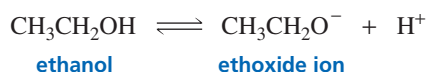
Although both the carboxylic acid and the carboxylate ion have delocalized electrons, the delocalization energy of the carboxylate ion is greater than that of the carboxylic acid because the ion has two equivalent resonance contributors that are predicted to be relatively stable, whereas the carboxylic acid has only one (Section 7.6). Therefore, loss of a proton from a carboxylic acid is accompanied by an increase in delocalization energy—in other words, an increase in stability.

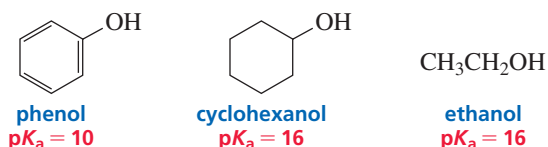
$$CH_3C(=O)OH \longleftrightarrow CH_3C(O^-)=\overset{+}{O}H \qquad CH_3C(=O)O^- \longleftrightarrow CH_3C(O^-)=O$$

relatively stable   relatively unstable   relatively stable   relatively stable

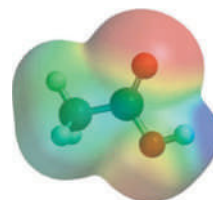
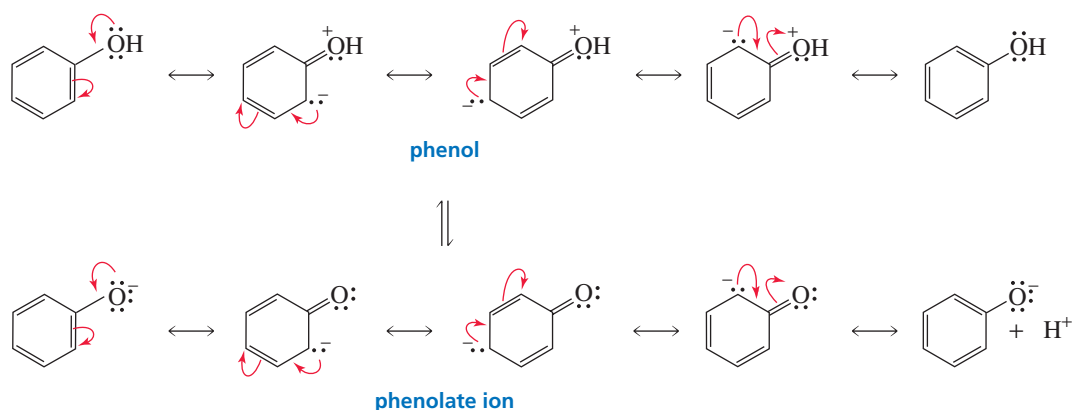
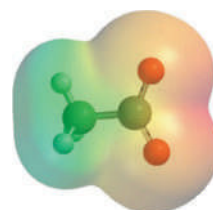
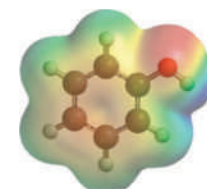
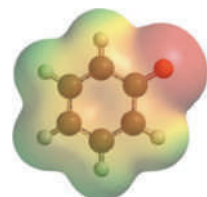
In contrast, all the electrons in both an alcohol and its conjugate base are localized, so loss of a proton from an alcohol is not accompanied by an increase in delocalization energy.

$$CH_3CH_2OH \rightleftharpoons CH_3CH_2O^- + H^+$$

ethanol   ethoxide ion

Phenol, a compound in which the OH group is bonded to a benzene ring, is a stronger acid than an alcohol such as cyclohexanol or ethanol.

phenol	cyclohexanol	CH_3CH_2OH ethanol
pK_a = 10	pK_a = 16	pK_a = 16

While both phenol and the phenolate ion have delocalized electrons, the delocalization energy of the phenolate ion is greater than that of phenol because three of phenol's resonance contributors have separated charges as well as a positive charge on an oxygen. The loss of a proton from phenol, therefore, is accompanied by an increase in delocalization energy (this is, greater stability).

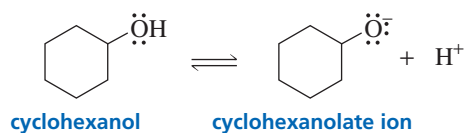
phenol

$\rightleftharpoons$

phenolate ion + H^+

phenol

phenolate ion

In contrast, the conjugate base of cyclohexanol does *not* have any delocalized electrons to stabilize it.

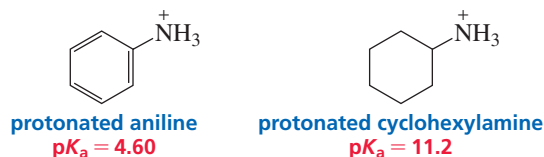
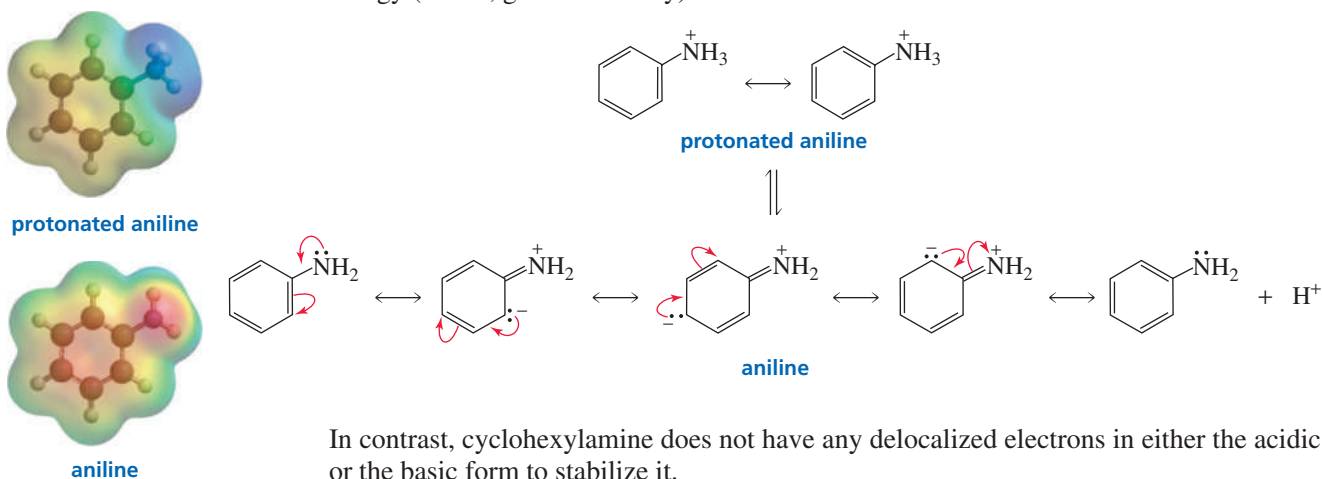
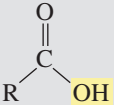
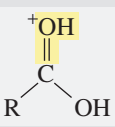
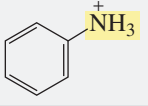
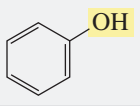
$$\text{cyclohexanol} \rightleftharpoons \text{cyclohexanolate ion} + H^+$$

cyclohexanol   cyclohexanolate ion

Phenol is a weaker acid than a carboxylic acid because the increased delocalization energy when a proton is lost is not as great in a phenolate ion as in a carboxylate ion, where the negative charge is shared equally by two oxygens.

Protonated aniline is a stronger acid than protonated cyclohexylamine.

$\overset{+}{N}H_3$ $\overset{+}{N}H_3$

protonated aniline
pK_a = 4.60

protonated cyclohexylamine
pK_a = 11.2

The nitrogen atom of protonated aniline lacks a lone pair that can be delocalized. However, when the nitrogen loses a proton, the lone pair that formerly held the proton can be delocalized. Loss of a proton, therefore, is accompanied by an increase in delocalization energy (that is, greater stability).

aniline

In contrast, cyclohexylamine does not have any delocalized electrons in either the acidic or the basic form to stabilize it.

$\overset{+}{N}H_3$ ⇌ $\ddot{N}H_2$ + H^+

protonated cyclohexylamine

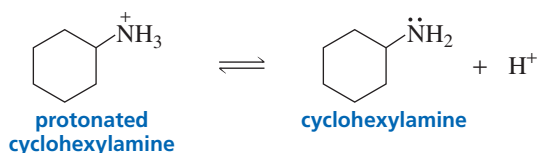
cyclohexylamine

We can now add phenol and protonated aniline to the list of organic compounds whose approximate pK_a values you should know (Table 7.1). They are also listed inside the front cover for easy reference.

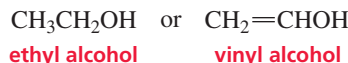
Table 7.1 Approximate pK_a Values

pK_a < 0	pK_a ≈ 5	pK_a ≈ 10	pK_a ≈ 15
$R\overset{+}{O}H$ (H)	$RC(=O)OH$	$R\overset{+}{N}H_3$	ROH
$RC(=\overset{+}{O}H)OH$	$C_6H_5\overset{+}{N}H_3$	C_6H_5OH	H_2O
H_3O^+			

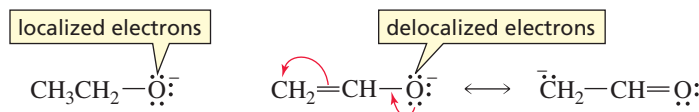
PROBLEM-SOLVING STRATEGY

Determining Relative Acidities

Which is a stronger acid?

$$\underset{\text{ethyl alcohol}}{CH_3CH_2OH} \quad \text{or} \quad \underset{\text{vinyl alcohol}}{CH_2{=}CHOH}$$

The strength of an acid depends on the stability of its conjugate base. We have seen that bases are stabilized by electron-withdrawing substituents and by electron delocalization. So you can answer the question by comparing the stabilities of the two conjugate bases and remembering that the more stable base will have the more acidic conjugate acid.

localized electrons: $CH_3CH_2{-}\ddot{\underset{..}{O}}{:}^-$

delocalized electrons: $CH_2{=}CH{-}\ddot{\underset{..}{O}}{:}^- \longleftrightarrow \bar{\ddot{C}}H_2{-}CH{=}\underset{..}{O}{:}$

All the electrons in ethanol's conjugate base are localized. However, vinyl alcohol's conjugate base is stabilized by electron delocalization. As a result, vinyl alcohol is a stronger acid than ethanol.

Now use the strategy you have just learned to solve Problem 11.

PROBLEM 11♦

Which member of each pair is the stronger acid?

a. $HC(=O)CH_2OH$ or $CH_3C(=O)OH$

b. $CH_3CH{=}CHCH_2OH$ or $CH_3CH{=}CHOH$

c. $CH_3CH_2CH_2\overset{+}{N}H_3$ or $CH_3CH{=}CH\overset{+}{N}H_3$

PROBLEM 12♦

Which member of each pair is the stronger base?

a. ethylamine or aniline

b. ethylamine or ethoxide ion

c. phenolate ion or ethoxide ion

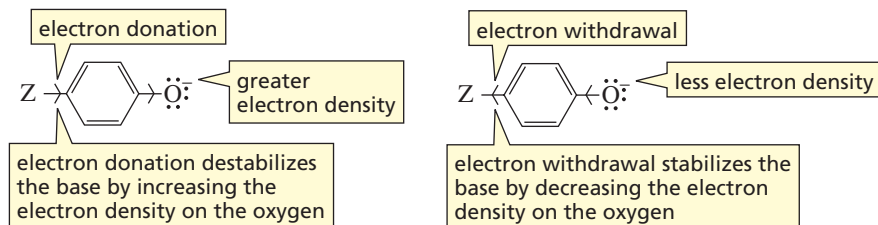
7.9 ELECTRONIC EFFECTS

If a substituent can withdraw electrons from or donate electrons to a benzene ring, then the pK_a values of substituted phenols, benzoic acids, and protonated anilines will change to reflect this withdrawal or donation.

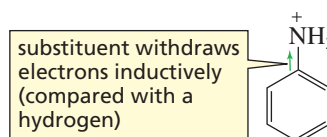
Electron-withdrawing groups stabilize a base and therefore increase the strength of its conjugate acid; electron-donating groups destabilize a base, which decreases the strength of its conjugate acid (Section 2.7). Remember: the stronger the acid, the more stable (weaker) its conjugate base.

electron withdrawal

less electron density

electron withdrawal stabilizes the base by decreasing the electron density on the oxygen

Electron donation decreases acidity. Electron withdrawal increases acidity.

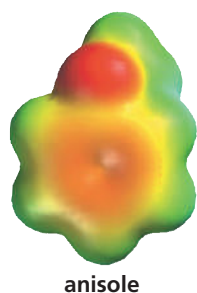
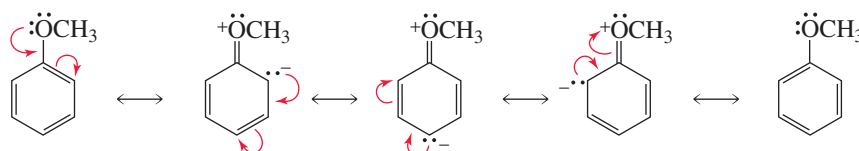
Inductive Electron Withdrawal

If a substituent that is bonded to a benzene ring is *more electron withdrawing than a hydrogen,* then it will draw the σ electrons away from the benzene ring more strongly than a hydrogen will. Withdrawal of electrons through a σ bond is called **inductive electron withdrawal** (Section 2.7). The $^{+}NH_3$ group is an example of a substituent that withdraws electrons inductively because it is more electronegative than a hydrogen.

Electron Donation by Hyperconjugation

We have seen that alkyl substituents (such as CH_3) stabilize carbocations by hyperconjugation—that is, by donating electrons to an empty *p* orbital (Section 6.2).

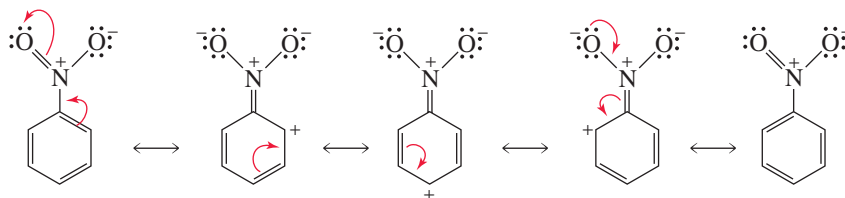
Electron Donation by Resonance

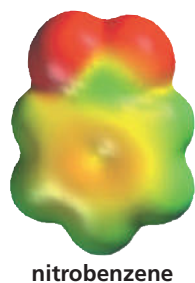
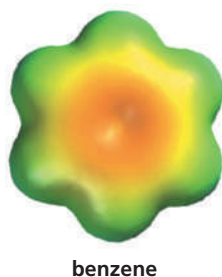
If a substituent has a lone pair on the atom directly attached to the benzene ring, then the lone pair can be delocalized into the ring. These substituents are said to **donate electrons by resonance.** Substituents such as NH_2, OH, OR, and Cl donate electrons by resonance. These substituents also withdraw electrons inductively because the atom attached to the benzene ring is more electronegative than a hydrogen.

anisole

Electron Withdrawal by Resonance

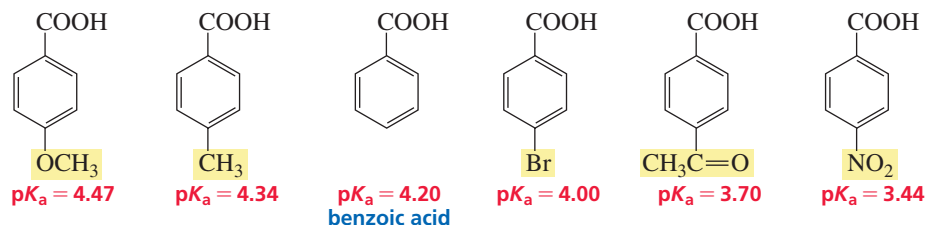
If a substituent is attached to the benzene ring by an atom that is doubly or triply bonded to a more electronegative atom, then the electrons of the ring can be delocalized onto the substituent; these substituents are said to **withdraw electrons by resonance.** Substituents such as C═O, C≡N, SO_3H, and NO_2 withdraw electrons by resonance. These substituents also withdraw electrons inductively because the atom attached to the benzene ring has a full or partial positive charge and is therefore more electronegative than a hydrogen.

benzene

withdrawal of electrons by resonance from a benzene ring

Take a minute to compare the electrostatic potential maps for anisole, benzene, and nitrobenzene. Notice that an electron-donating substituent (OCH_3) makes the ring more red (more negative), whereas an electron-withdrawing substituent (NO_2) makes the ring less red (less negative).

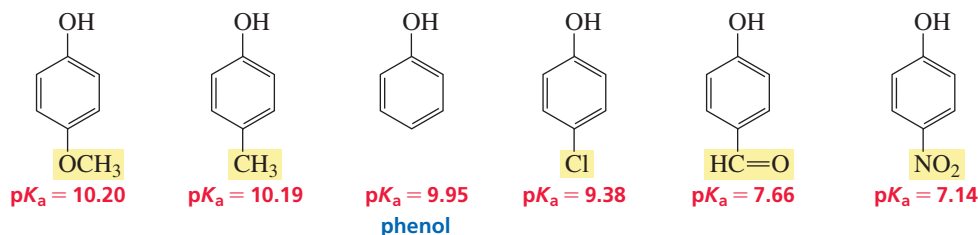
nitrobenzene

Now let's look at how substituents affect the pK_a of benzoic acid.

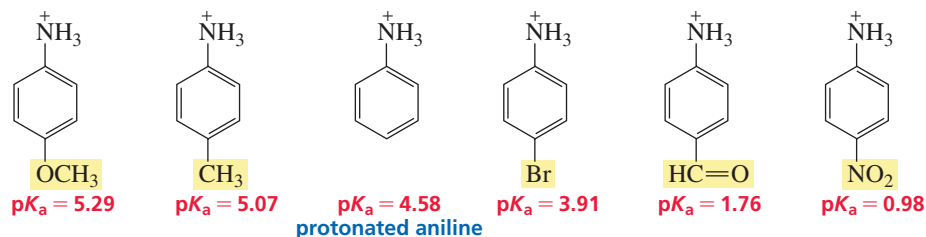
We have seen that a methyl group donates electrons by *hyperconjugation*. This causes methyl-substituted benzoic acid to be a weaker acid than benzoic acid. Because the methoxy group (CH_3O) has a lone pair on the atom attached to the ring, it can *donate electrons by resonance*. Because oxygen is more electronegative than hydrogen, the methoxy group *withdraws electrons inductively*. The fact that methoxy-substituted benzoic acid is a weaker acid than benzoic acid indicates that the substituent's resonance electron donation into the ring is more significant than its inductive electron withdrawal from the ring.

COOH / OCH_3	COOH / CH_3	COOH	COOH / Br	COOH / $CH_3C{=}O$	COOH / NO_2
pK_a = 4.47	pK_a = 4.34	pK_a = 4.20 benzoic acid	pK_a = 4.00	pK_a = 3.70	pK_a = 3.44

A Br also has a lone pair that can *donate electrons by resonance* and, because it is more electronegative than hydrogen, Br *withdraws electrons inductively*. The fact that bromo-substituted benzoic acid is a stronger acid than benzoic acid indicates that Br's inductive electron withdrawal from the ring is more significant than its resonance electron donation into the ring.

The HC=O and NO_2 groups *withdraw electrons both by resonance* and *inductively*. Therefore, these substituents increase the acidity of benzoic acid. Recall that a NO_2 group has a positive charge on the nitrogen (see page 260), which causes it to strongly withdraw electrons. This is reflected in the pK_a value of nitro-substituted benzoic acid.

A similar substituent effect on pK_a is observed for substituted phenols and substituted protonated anilines—that is, electron-withdrawing substituents increase acidity, whereas electron-donating substituents decrease acidity.

OH / OCH_3	OH / CH_3	OH	OH / Cl	OH / HC=O	OH / NO_2
pK_a = 10.20	pK_a = 10.19	pK_a = 9.95 phenol	pK_a = 9.38	pK_a = 7.66	pK_a = 7.14

The more electron donating the substituent, the more it decreases the acidity of a COOH, an OH, or an $^+NH_3$ group attached to a benzene ring.

$\overset{+}{N}H_3$ / OCH_3	$\overset{+}{N}H_3$ / CH_3	$\overset{+}{N}H_3$	$\overset{+}{N}H_3$ / Br	$\overset{+}{N}H_3$ / HC=O	$\overset{+}{N}H_3$ / NO_2
pK_a = 5.29	pK_a = 5.07	pK_a = 4.58 protonated aniline	pK_a = 3.91	pK_a = 1.76	pK_a = 0.98

The more electron withdrawing the substituent, the more it increases the acidity of a COOH, an OH, or an $^+NH_3$ group attached to a benzene ring.

PROBLEM 13♦

For each of the following substituents, indicate whether it withdraws electrons inductively, donates electrons by hyperconjugation, withdraws electrons by resonance, or donates electrons by resonance. (Effects should be compared with that of a hydrogen; remember that many substituents can be characterized in more than one way.)

a. Br **b.** CH_2CH_3 **c.** $\overset{O}{\overset{\|}{C}}CH_3$ **d.** $NHCH_3$ **e.** OCH_3 **f.** $^+N(CH_3)_3$

PROBLEM 14♦

Which species in each of the following pairs is more acidic?

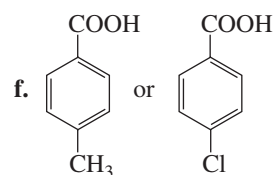
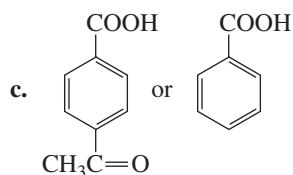
a. CH_3COOH or $ClCH_2COOH$

b. O_2NCH_2COOH or $O_2NCH_2CH_2COOH$

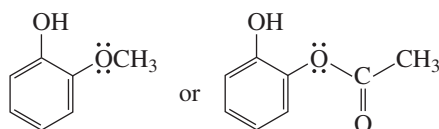
c. (4-acetylbenzoic acid, with COOH and $CH_3C{=}O$ substituents) or (benzoic acid, COOH)

d. CH_3CH_2COOH or $H_3\overset{+}{N}CH_2COOH$

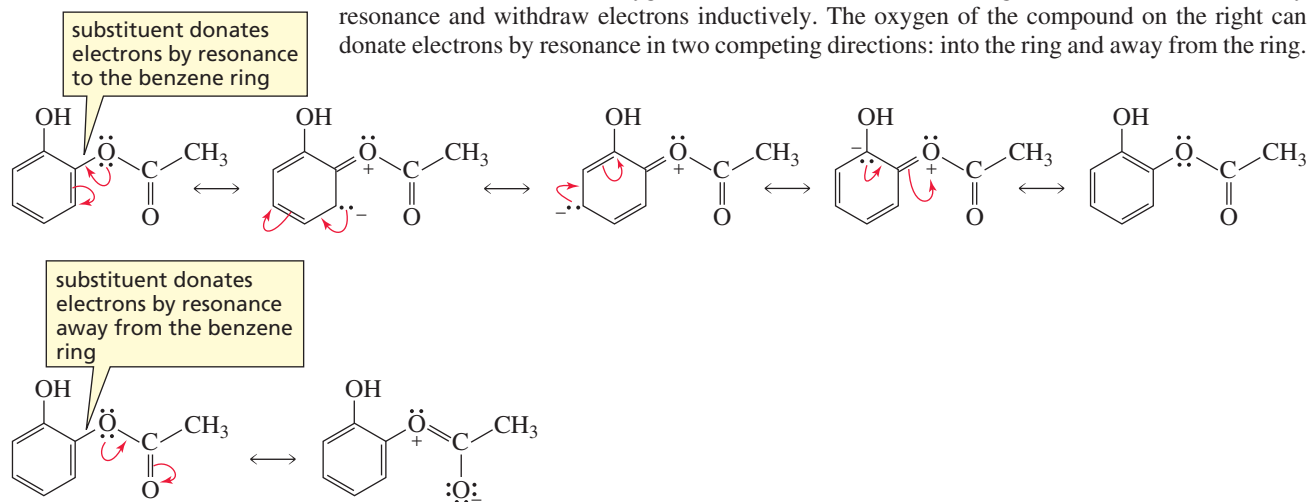
e. $HCOOH$ or CH_3COOH

f. (4-methylbenzoic acid, COOH and CH_3) or (4-chlorobenzoic acid, COOH and Cl)

PROBLEM 15 Solved

Which is a stronger acid?

OH / $\ddot{O}CH_3$ or OH / $\ddot{O}$–C(=O)–CH_3

Both substituents have an oxygen atom attached to a benzene ring that can donate electrons by resonance and withdraw electrons inductively. The oxygen of the compound on the right can donate electrons by resonance in two competing directions: into the ring and away from the ring.

substituent donates electrons by resonance to the benzene ring

substituent donates electrons by resonance away from the benzene ring

In contrast, the methoxy substituent (CH_3O) can donate electrons by resonance only into the ring (see page 260).

Therefore, overall the methoxy substituent is better at donating electrons, so the compound on the right is the stronger acid.

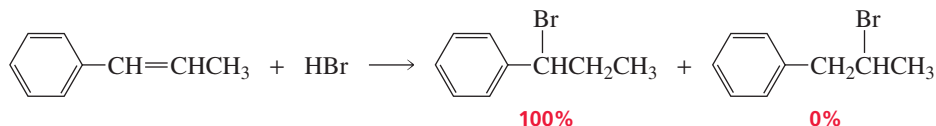
PROBLEM 16

Explain why the pK_a of *p*-nitrophenol is 7.14, whereas the pK_a of *m*-nitrophenol is 8.39. (*Hint:* Draw the resonance contributors.)

7.10 DELOCALIZED ELECTRONS CAN AFFECT THE PRODUCT OF A REACTION

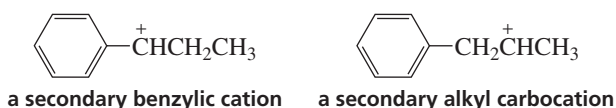
Our ability to correctly predict the product of an organic reaction often depends on recognizing when organic molecules have delocalized electrons. For example, the alkene in the following reaction has the same number of hydrogens on both of its sp^2 carbons:

$$C_6H_5-CH{=}CHCH_3 + HBr \longrightarrow C_6H_5-\underset{Br}{CH}CH_2CH_3 + C_6H_5-CH_2\underset{Br}{CH}CH_3$$

100%   0%

Therefore, the rule that tells us to add the electrophile to the sp^2 carbon bonded to the most hydrogens predicts that approximately equal amounts of the two products will be formed. When the reaction is carried out, however, we find that only one of the products is formed. (Notice that the stability of the benzene ring prevents its double bonds from undergoing electrophilic addition reactions. See Section 7.13.)

The rule leads us to an incorrect prediction of the reaction product because it does not take electron delocalization into consideration. It presumes that both carbocation intermediates are equally stable since they are both secondary carbocations. It does not take into account that one is a secondary alkyl carbocation, whereas the other is a secondary benzylic cation. Because the secondary benzylic cation is stabilized by electron delocalization, it is more stable and therefore formed more readily. The difference in the stabilities of the carbocations, and therefore their rates of formation, is sufficient to cause only one product to be obtained.

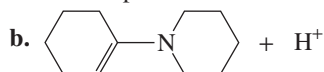
$C_6H_5\overset{+}{C}HCH_2CH_3$ **a secondary benzylic cation**

$C_6H_5CH_2\overset{+}{C}HCH_3$ **a secondary alkyl carbocation**

Let this example serve as a warning. The rule that states that the electrophile adds to the sp^2 carbon bonded to the most hydrogens cannot be applied to reactions that form carbocations that can be stabilized by electron delocalization. In such cases, you must look at the relative stabilities of the individual carbocations to predict the major product of the reaction.

PROBLEM 17 Solved

Predict the sites on each of the following compounds where protonation can occur.

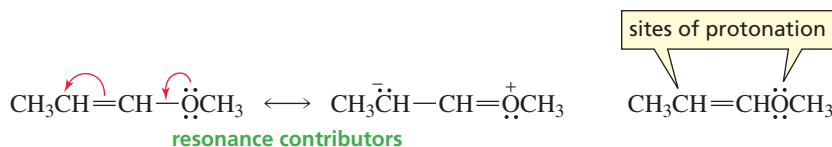
a. $CH_3CH{=}CHOCH_3 + H^+$

b. (cyclohexenyl)–N(piperidine) + H^+

Solution to 17a The resonance contributors reveal that there are two sites that can be protonated: the lone pair on oxygen and the lone pair on carbon.

$$CH_3CH{=}CH{-}\ddot{O}CH_3 \longleftrightarrow CH_3\bar{\ddot{C}}H{-}CH{=}\overset{+}{O}CH_3$$

resonance contributors

$$CH_3CH{=}CH\ddot{O}CH_3$$

sites of protonation

7.11 REACTIONS OF DIENES

For another example of how delocalized electrons can affect the product of a reaction, we will compare the products formed when *isolated dienes* (dienes that have only localized electrons) undergo electrophilic addition reactions to the products formed when *conjugated dienes* (dienes that have delocalized electrons) undergo the same reactions.

$CH_2{=}CHCH_2CH_2CH{=}CH_2$ **an isolated diene**

$CH_3CH{=}CH{-}CH{=}CHCH_3$ **a conjugated diene**

Reactions of Isolated Dienes

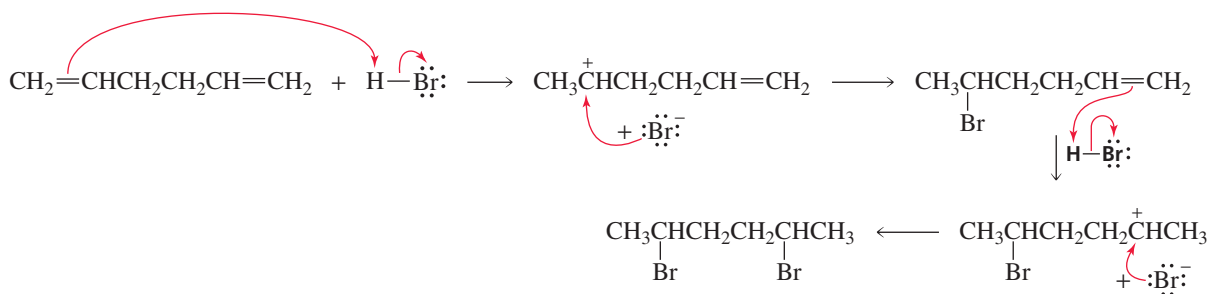
The reactions of *dienes with isolated double bonds* are just like the reactions of alkenes. If an excess of the electrophilic reagent is present, two independent electrophilic addition reactions will occur. In each reaction, *the electrophile adds to the* sp^2 *carbon bonded to the most hydrogens.*

$$\underset{\text{1,5-hexadiene}}{CH_2{=}CHCH_2CH_2CH{=}CH_2} + \underset{\text{excess}}{HBr} \longrightarrow CH_3\underset{Br}{C}HCH_2CH_2\underset{Br}{C}HCH_3$$

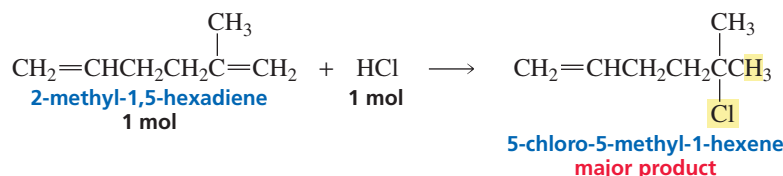
The reaction proceeds exactly as we would predict from our knowledge of the mechanism for the reaction of alkenes with electrophilic reagents.

MECHANISM FOR THE REACTION OF AN ISOLATED DIENE WITH EXCESS HBr

$$CH_2{=}CHCH_2CH_2CH{=}CH_2 + H{-}\ddot{Br}: \longrightarrow CH_3\overset{+}{C}HCH_2CH_2CH{=}CH_2 + :\ddot{Br}:^- \longrightarrow CH_3CH(Br)CH_2CH_2CH{=}CH_2$$

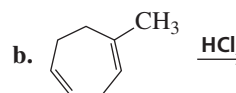
$$\xrightarrow{H-\ddot{Br}:} CH_3CH(Br)CH_2CH_2\overset{+}{C}HCH_3 + :\ddot{Br}:^- \longrightarrow CH_3CH(Br)CH_2CH_2CH(Br)CH_3$$

- The electrophile (H^+) adds to the sp^2 carbon bonded to the most hydrogens in order to form the more stable carbocation (Section 6.3).
- The bromide ion adds to the carbocation.
- Because there is an excess of the electrophilic reagent, there is enough reagent to add to the other double bond; again the H^+ adds to the sp^2 carbon bonded to the most hydrogens.
- The bromide ion adds to the carbocation.

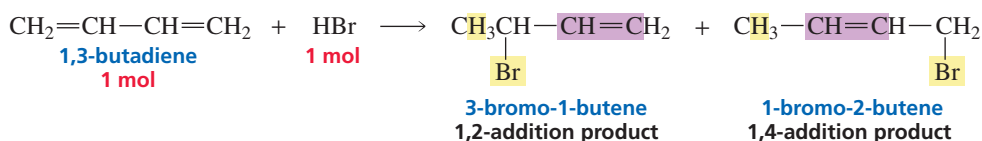
If there is only enough electrophilic reagent to add to one of the double bonds, it will add preferentially to the more reactive one. For example, in the following reaction, addition of HCl to the double bond on the left forms a secondary carbocation, whereas addition to the double bond on the right forms a tertiary carbocation. Because the tertiary carbocation is more stable and is therefore formed faster, the major product of the reaction will be 5-chloro-5-methyl-1-hexene in the presence of a limited amount of HCl (Section 6.3).

$$\underset{\text{2-methyl-1,5-hexadiene, 1 mol}}{CH_2{=}CHCH_2CH_2C(CH_3){=}CH_2} + \underset{\text{1 mol}}{HCl} \longrightarrow \underset{\text{5-chloro-5-methyl-1-hexene, major product}}{CH_2{=}CHCH_2CH_2C(CH_3)(Cl)CH_3}$$

PROBLEM 18♦

What is the major product of each of the following reactions, assuming that one equivalent of each reagent is used in each reaction?

a. $CH_2{=}CHCH_2CH_2CH{=}C(CH_3)CH_3 \xrightarrow{HBr}$

b. 1-methylcycloheptene (ring with CH_3) $\xrightarrow{HCl}$

Reactions of Conjugated Dienes

When a diene with *conjugated double bonds*, such as 1,3-butadiene, reacts with a limited amount of electrophilic reagent so that addition can occur at only one of the double bonds, two addition products are formed. One is a **1,2-addition product**—the result of addition at the 1- and 2-positions. The other is a **1,4-addition product**—the result of addition at the 1- and 4-positions. 1,2-Addition is called **direct addition,** and 1,4-addition is called **conjugate addition.**

An isolated diene undergoes only 1,2-addition.

A conjugated diene undergoes both 1,2- and 1,4-addition.

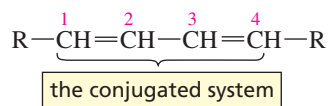
$$\underset{\text{1,3-butadiene, 1 mol}}{CH_2{=}CH{-}CH{=}CH_2} + \underset{\text{1 mol}}{HBr} \longrightarrow \underset{\text{3-bromo-1-butene, 1,2-addition product}}{CH_3CH(Br){-}CH{=}CH_2} + \underset{\text{1-bromo-2-butene, 1,4-addition product}}{CH_3{-}CH{=}CH{-}CH_2Br}$$

Based on your knowledge of how hydrogen halides add to double bonds, you would expect the 1,2-addition product. The 1,4-addition product, however, is surprising,

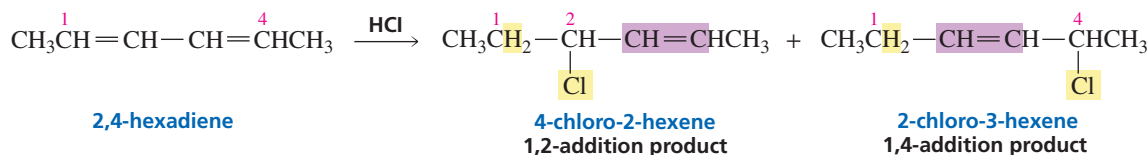
because the reagent did not add to adjacent carbons and a double bond changed its position.

When we talk about addition at the 1- and 2-positions or at the 1- and 4-positions, the numbers refer to the four carbons of the conjugated system. Thus, the carbon in the 1-position is one of the sp^2 carbons at the end of the conjugated system—it is not necessarily the first carbon in the molecule.

$$R-\overset{1}{C}H=\overset{2}{C}H-\overset{3}{C}H=\overset{4}{C}H-R$$

the conjugated system

For example, the 1- and 4-positions in the conjugated system of 2,4-hexadiene are actually C-2 and C-5.

$$CH_3\overset{1}{C}H=CH-CH=\overset{4}{C}HCH_3 \xrightarrow{HCl} CH_3\overset{1}{C}H_2-\overset{2}{C}H(Cl)-CH=CHCH_3 + CH_3\overset{1}{C}H_2-CH=CH-\overset{4}{C}H(Cl)CH_3$$

2,4-hexadiene → 4-chloro-2-hexene (1,2-addition product) + 2-chloro-3-hexene (1,4-addition product)

To understand why an electrophilic addition reaction to a conjugated diene forms both 1,2-addition and 1,4-addition products, we need to look at the mechanism of the reaction.

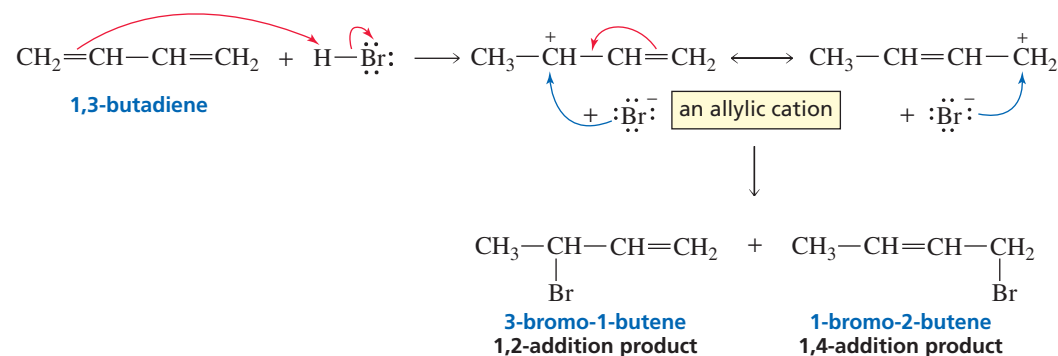
MECHANISM FOR THE REACTION OF A CONJUGATED DIENE WITH HBr

$$CH_2=CH-CH=CH_2 + H-\ddot{Br}: \longrightarrow CH_3-\overset{+}{C}H-CH=CH_2 \longleftrightarrow CH_3-CH=CH-\overset{+}{C}H_2$$

1,3-butadiene; an allylic cation; $+ :\ddot{Br}:^-$

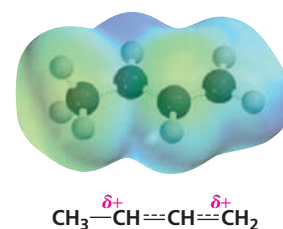
$$\downarrow$$

$$CH_3-CH(Br)-CH=CH_2 + CH_3-CH=CH-CH_2Br$$

3-bromo-1-butene (1,2-addition product) + 1-bromo-2-butene (1,4-addition product)

- The proton adds to C-1, forming an allylic cation. The allylic cation has delocalized electrons.
- The resonance contributors of the allylic cation show that the positive charge is shared by C-2 and C-4. Consequently, the bromide ion can add to either C-2 or C-4 to form the 1,2-addition product or the 1,4-addition product.

$$CH_3-\overset{\delta+}{C}H\text{---}CH\text{---}\overset{\delta+}{C}H_2$$

Notice that, in the first step of the reaction, adding H^+ to C-1 is the same as adding it to C-4 because 1,3-butadiene is symmetrical.

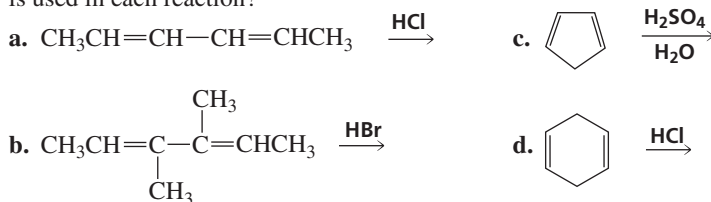
As we look at more examples, notice that the first step in all electrophilic additions to conjugated dienes is the addition of the electrophile to one of the sp^2 carbons *at the end of the conjugated system*. This is the only way to form a carbocation that is stabilized by electron delocalization. If the electrophile were to add to one of the internal sp^2 carbons, the resulting carbocation would not have delocalized electrons, so it would be less stable.

PROBLEM 19♦

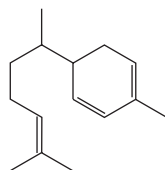
What are the products of the following reactions, assuming that one equivalent of each reagent is used in each reaction?

a. $CH_3CH=CH-CH=CHCH_3 \xrightarrow{HCl}$

b. $CH_3CH=C(CH_3)-C(CH_3)=CHCH_3 \xrightarrow{HBr}$

c. (cyclopentadiene) $\xrightarrow[H_2O]{H_2SO_4}$

d. (1,3-cyclohexadiene) $\xrightarrow{HCl}$

PROBLEM 20♦

Which of the double bonds in zingiberene, the compound responsible for the aroma of ginger, is the most reactive in an electrophilic addition reaction with HBr?

zingiberene ginger

PROBLEM 21

What stereoisomers are obtained from the reaction whose mechanism is shown on page 265 and the reaction shown on the top of page 265? (*Hint:* Review Section 6.5.)

PROBLEM 22

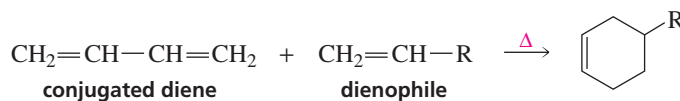
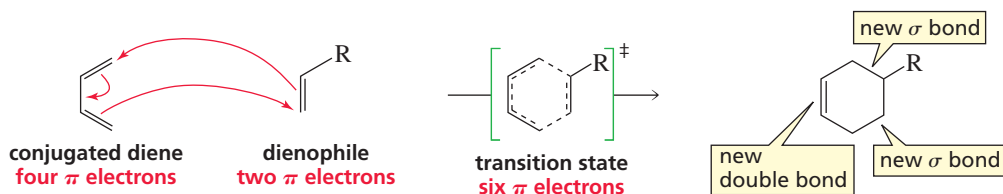
What products would be obtained from the reaction of 1,3,5-hexatriene with one equivalent of HBr? Disregard stereoisomers.

7.12 THE DIELS–ALDER REACTION IS A 1,4-ADDITION REACTION

Reactions that create new carbon–carbon bonds are very important to synthetic organic chemists because it is only through such reactions that small carbon skeletons can be converted into larger ones. The Diels–Alder reaction is a particularly important reaction because it creates *two* new carbon–carbon bonds and in the process forms a cyclic compound. In recognition of the importance of this reaction to synthetic organic chemistry, Otto Diels and Kurt Alder shared the Nobel Prize in Chemistry in 1950.

In a **Diels–Alder reaction,** a conjugated diene reacts with a compound containing a carbon–carbon double bond. The latter compound is called a **dienophile** because it "loves a diene." (Δ signifies heat.)

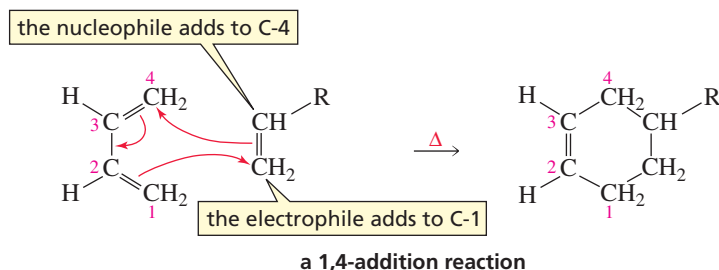
$$CH_2{=}CH{-}CH{=}CH_2 + CH_2{=}CH{-}R \xrightarrow{\Delta}$$

conjugated diene dienophile

MECHANISM FOR THE DIELS–ALDER REACTION

- Although this reaction may not look like any reaction you have seen before, it is simply the 1,4-addition of an electrophile and a nucleophile to a conjugated diene. However, unlike the other 1,4-addition reactions you have seen—where the electrophile adds to the diene in the first step and the nucleophile adds to the carbocation in the second step—in the Diels–Alder reaction, the addition of the electrophile and the addition of the nucleophile occur in the same step.

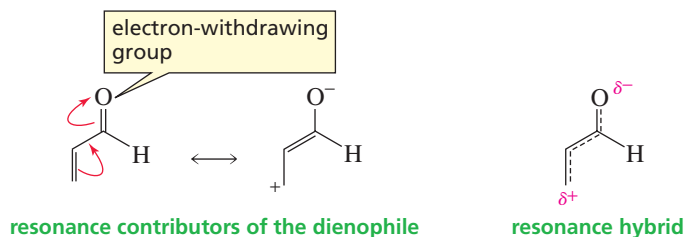
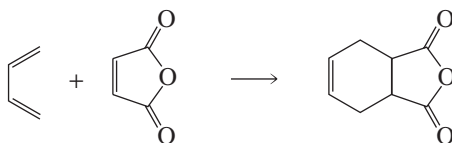
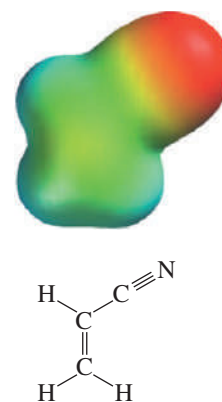
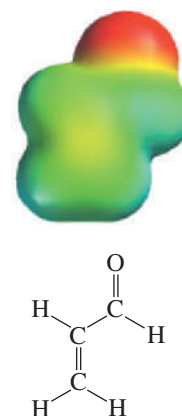
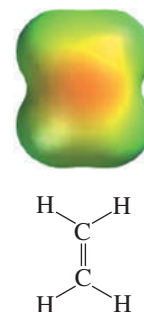
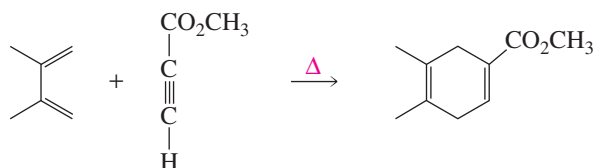
The Diels-Alder reaction looks odd at first glance because the electrophile and the nucleophile that add to the conjugated diene are the adjacent sp^2 carbons of a double bond. As with other 1,4-addition reactions, the double bond in the product is between the 2- and 3-positions of the diene's conjugated system.

the nucleophile adds to C-4

the electrophile adds to C-1

a 1,4-addition reaction

The reactivity of the dienophile is increased if an electron-withdrawing group is attached to one of its sp^2 carbons. An electron-withdrawing group, such as a carbonyl group (C═O) or a cyano group (C≡N), withdraws electrons from the dienophile's double bond. This puts a partial positive charge on the sp^2 carbon that the π electrons of the conjugated diene add to. Thus, the electron-withdrawing group makes the dienophile a better electrophile (Figure 7.2).

electron-withdrawing group

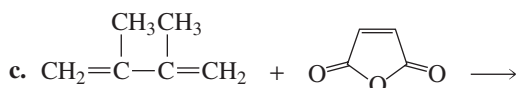
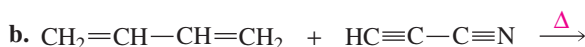
resonance contributors of the dienophile **resonance hybrid**

A wide variety of cyclic compounds can be obtained by varying the structures of the conjugated diene and the dienophile.

Compounds containing carbon–carbon triple bonds can also be used as dienophiles in Diels–Alder reactions to prepare compounds with two isolated double bonds.

▲ **Figure 7.2**
The bluish color at the bottom of these electrostatic potential maps shows that an electron-withdrawing substituent makes the bottom sp^2 carbon a better electrophile.

PROBLEM 23♦

What are the products of the following reactions?

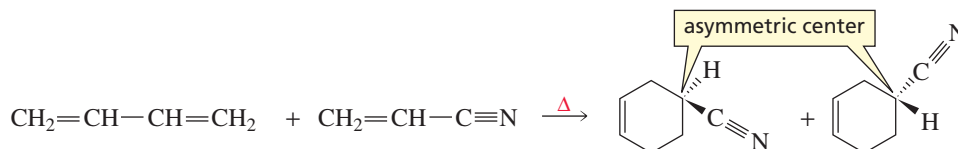
a. $CH_2{=}CH{-}CH{=}CH_2 + CH_3C(=O){-}C{\equiv}C{-}C(=O)CH_3 \xrightarrow{\Delta}$

b. $CH_2{=}CH{-}CH{=}CH_2 + HC{\equiv}C{-}C{\equiv}N \xrightarrow{\Delta}$

c. $CH_2{=}C(CH_3){-}C(CH_3){=}CH_2$ + maleic anhydride $\longrightarrow$

The Stereochemistry of the Diels–Alder Reaction

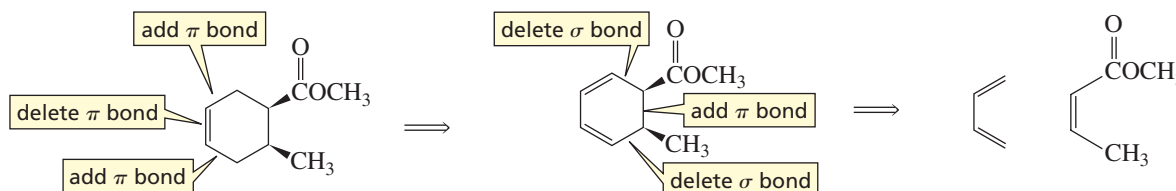
As with all the other reactions we have seen, if a Diels–Alder reaction creates a product with an asymmetric center, the product will be a racemic mixture (Section 6.5).

$$CH_2{=}CH{-}CH{=}CH_2 + CH_2{=}CH{-}C{\equiv}N \xrightarrow{\Delta}$$

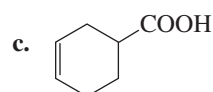
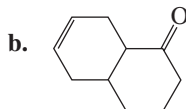
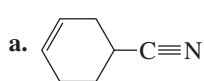
asymmetric center

Retrosynthetic Analysis of the Diels–Alder Reaction

To determine the reactants needed to synthesize a Diels-Alder product:

1. Locate the double bond in the product. The diene that was used to form the cyclic product had double bonds on either side of this double bond, so draw in those double bonds and remove the original double bond.
2. The new σ bonds are now on the other side of these new double bonds. Deleting these σ bonds and putting a π bond between the two carbons whose σ bonds were deleted gives the needed reactants—that is, the diene and the dienophile.

add π bond
delete π bond
add π bond
$COCH_3$
CH_3
delete σ bond
add π bond
delete σ bond
$COCH_3$
CH_3

PROBLEM 24♦

What diene and what dienophile should be used to synthesize the following?

a. C≡N **b.** **c.** COOH

7.13 BENZENE IS AN AROMATIC COMPOUND

The two resonance contributors of benzene are identical, so we expect benzene to have a relatively large delocalization energy (Section 7.6).

Aromatic compounds are particularly stable.

The heat of hydrogenation data shown in Figure 7.3 indicate that benzene's delocalization energy very large (36 kcal/mol). Compounds with large delocalization energies, such as benzene, are called **aromatic compounds.**

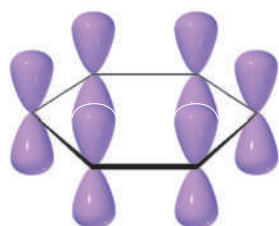
Because of its large delocalization energy, benzene is an extremely stable compound. Therefore, it does not undergo the electrophilic addition reactions that are characteristic of alkenes. (Notice the conditions that had to be used to reduce benzene's double bonds; page 244.) Now we can understand why benzene's unusual stability puzzled nineteenth-century chemists, who did not know about delocalized electrons (Section 7.1).

▲ **Figure 7.3**
Cyclohexene, a compound with one double bond with *localized* π electrons, has an experimental $\Delta H° = -28.6$ kcal/mol for its reaction with H_2 to form cyclohexane. Therefore, the $\Delta H°$ of "cyclohexatriene," an unknown hypothetical compound with three double bonds with *localized* π electrons, would be three times that value ($\Delta H° = 3 \times -28.6 = -85.8$) for the same reaction. Benzene, which has three double bonds with *delocalized* π electrons, has an experimental $\Delta H° = -49.8$ kcal/mol for its reaction with H_2 to form cyclohexane. The difference in the energies of "cyclohexatriene" and benzene (36 kcal/mol) is the delocalization energy of benzene—the extra stability benzene has as a result of having delocalized electrons.

7.14 THE TWO CRITERIA FOR AROMATICITY

How can we tell whether a compound is aromatic by looking at its structure? In other words, what structural features do aromatic compounds have in common? To be classified as aromatic, a compound must meet both of the following criteria:

1. *It must have an uninterrupted cyclic cloud of π electrons* (called a π cloud) *above and below the plane of the molecule*. Let's look a little more closely at what this means:
   - For the π cloud to be cyclic, *the molecule must be cyclic.*
   - For the π cloud to be uninterrupted, *every atom in the ring must have a* p *orbital.*
   - For the π cloud to form, each *p* orbital must overlap the *p* orbitals on either side of it. As a result, *the molecule must be planar*.
2. *The π cloud must contain an odd number of pairs of π electrons.*

Thus, benzene is an aromatic compound because it is cyclic and planar, every carbon in the ring has a *p* orbital, and the π cloud contains *three* pairs of π electrons (Figure 7.1).

benzene's *p* orbitals

benzene's π cloud

benzene has 3 pairs of π electrons

For a compound to be aromatic, it must be cyclic and planar, and it must have an uninterrupted cloud of π electrons. The π cloud must contain an odd number of pairs of π electrons.

7.15 APPLYING THE CRITERIA FOR AROMATICITY

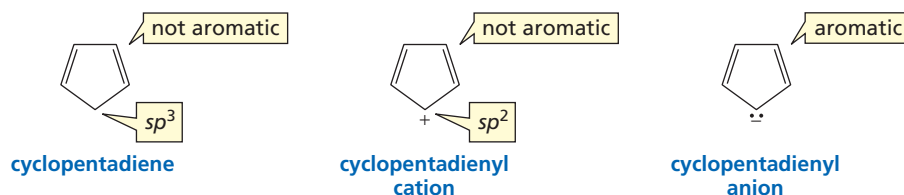
Cyclobutadiene has two pairs of π electrons, and cyclooctatetraene has four pairs of π electrons. These compounds, therefore, are *not* aromatic because they have an *even* number of pairs of π electrons. There is an additional reason cyclooctatetraene is not aromatic—it is not planar; it is tub shaped (see page 247). Because cyclobutadiene and cyclooctatetraene are not aromatic, they do not have the unusual stability of aromatic compounds.

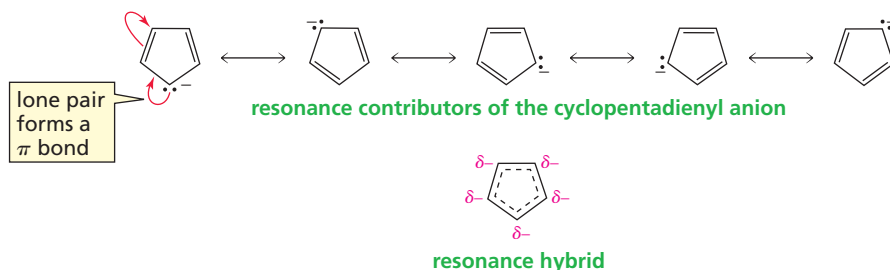
cyclobutadiene **cyclooctatetraene**

Now let's look at some other compounds and determine whether they are aromatic. Cyclopentadiene is not aromatic because it does not have an uninterrupted ring of *p* orbital-bearing atoms. One of its ring atoms is sp^3 hybridized, and only sp^2 and *sp* carbons have *p* orbitals. Therefore, cyclopentadiene does not fulfill the first criterion for aromaticity.

not aromatic
sp^3
cyclopentadiene

not aromatic
sp^2
cyclopentadienyl cation

aromatic
cyclopentadienyl anion

The cyclopentadienyl cation is not aromatic either, because although it has an uninterrupted ring of *p* orbital-bearing atoms, its π cloud has an even number of pairs (two) of π electrons. The cyclopentadienyl anion, on the other hand, is aromatic: it has an uninterrupted ring of *p* orbital-bearing atoms, and the π cloud contains an odd number of pairs (three) of delocalized π electrons.

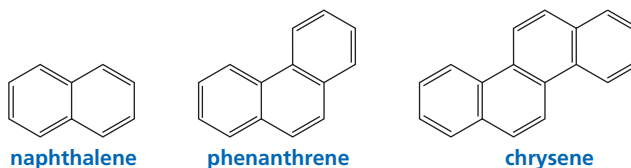
How do we know that the cyclopentadienyl anion's lone-pair electrons are π electrons? There is an easy way to determine this: if a lone pair can be used to form a π bond in the ring of a resonance contributor of the compound, then the lone-pair electrons are π electrons.

When drawing resonance contributors, remember that only electrons move; atoms never move.

resonance contributors of the cyclopentadienyl anion

resonance hybrid

The resonance hybrid shows that all the carbons in the cyclopentadienyl anion are equivalent. Each carbon has exactly one-fifth of the negative charge associated with the anion.

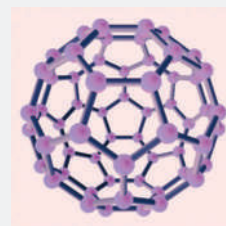
The criteria that determine whether a monocyclic hydrocarbon is aromatic can also be used to determine whether a polycyclic hydrocarbon is aromatic. Naphthalene (five pairs of π electrons), phenanthrene (seven pairs of π electrons), and chrysene (nine pairs of π electrons) are aromatic.

naphthalene **phenanthrene** **chrysene**

Buckyballs

We have seen that diamond, graphite, and graphene are forms of pure carbon (Section 1.8). Another form was discovered unexpectedly in 1985, while scientists were conducting experiments designed to understand how long-chain molecules are formed in outer space. R. E. Smalley, R. F. Curl, Jr., and H. W. Kroto shared the 1996 Nobel Prize in Chemistry for discovering this new form of carbon. They named the substance *buckminsterfullerene* (often shortened to *fullerene*) because its structure reminded them of the geodesic domes popularized by R. Buckminster Fuller, an American architect and philosopher. Buckminsterfullerene's nickname is "buckyball."

Consisting of a hollow cluster of 60 carbons, fullerene is the most symmetrical large molecule known. Like graphite and graphene, fullerene has only sp^2 carbons, but instead of being arranged in layers, the carbons are arranged in rings that fit together like the seams of a soccer ball. Each molecule has 32 interlocking rings (20 hexagons and 12 pentagons). At first glance, fullerene appears to be aromatic because of its benzene-like rings. However, the curvature of the ball prevents the molecule from fulfilling the first criterion for aromaticity—that it must be planar. Therefore, fullerene is not aromatic.

Buckyballs have extraordinary chemical and physical properties. For example, they are exceedingly rugged, as shown by their ability to survive the extreme temperatures of outer space. Because they are essentially hollow cages, they can be manipulated to make new materials. For example, when a buckyball is "doped" with potassium or cesium, it becomes an excellent organic superconductor. These molecules are now being studied for use in many other applications, including the development of new polymers, catalysts, and drug-delivery systems. The discovery of buckyballs is a strong reminder of the technological advances that can be achieved as a result of basic research.

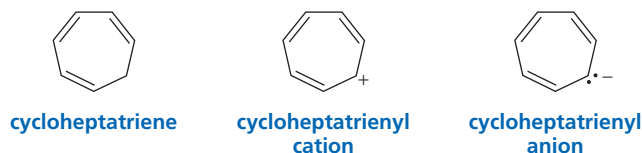
a geodesic dome

C_{60}
buckminsterfullerene
"buckyball"

PROBLEM 25♦

Which compound is aromatic? Explain your choice.

cycloheptatriene

cycloheptatrienyl cation

cycloheptatrienyl anion

PROBLEM 26 Solved

The pK_a of cyclopentane is > 60, which is about what is expected for a hydrogen that is bonded to an sp^3 carbon. Explain why cyclopentadiene is a much stronger acid (pK_a = 15), even though it too involves the loss of a proton from an sp^3 carbon.

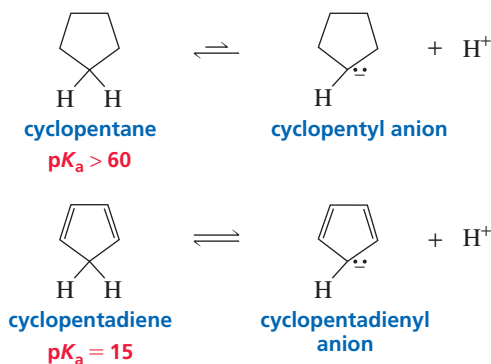
cyclopentane ⇌ cyclopentyl anion + H^+

cyclopentane
pK_a > 60

cyclopentyl anion

cyclopentadiene ⇌ cyclopentadienyl anion + H^+

cyclopentadiene
pK_a = 15

cyclopentadienyl anion

Solution To answer this question, we must look at the stabilities of the anions that are formed when the compounds lose a proton. (Recall that the strength of an acid is determined by the stability of its conjugate base: the more stable the base, the stronger its conjugate acid; Section 2.6). All the electrons in the cyclopentyl anion are localized. In contrast, the cyclopentadienyl anion is aromatic. As a result of its aromaticity, the cyclopentadienyl anion is an unusually stable carbanion, causing its conjugate acid to be an unusually strong acid compared to other compounds with hydrogens attached to sp^3 carbons.

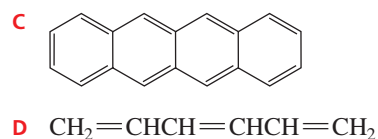
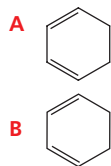
PROBLEM 27♦

Which of the following are aromatic?

A (cyclohexadiene structure)

B (cyclohexadienyl cation structure, +)

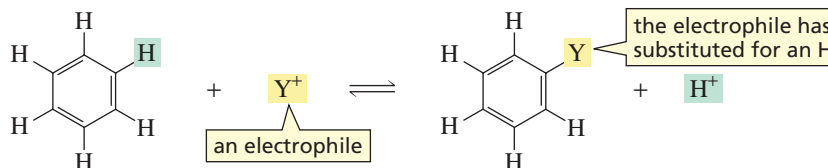
C (fused four-ring aromatic structure)

D $CH_2{=}CHCH{=}CHCH{=}CH_2$

7.16 HOW BENZENE REACTS

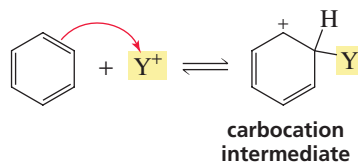
Aromatic compounds such as benzene undergo **electrophilic aromatic substitution reactions:** an electrophile substitutes for one of the hydrogens attached to the benzene ring.

$$C_6H_6 + Y^+ \rightleftharpoons C_6H_5Y + H^+$$

an electrophile

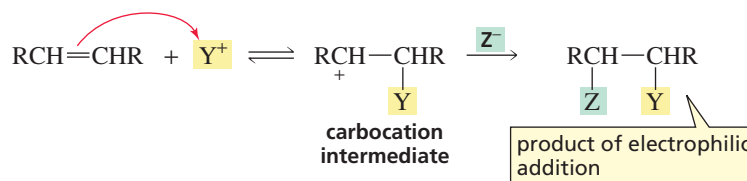
the electrophile has substituted for an H

Now let's look at why this substitution reaction occurs. The cloud of π electrons above and below the plane of its ring makes benzene a nucleophile, so it reacts with an electrophile (Y^+). When an electrophile attaches itself to a benzene ring, a carbocation intermediate is formed.

$$C_6H_6 + Y^+ \rightleftharpoons \text{carbocation intermediate}$$

carbocation intermediate

This description should remind you of the first step in an *electrophilic addition reaction* of an alkene: the nucleophilic alkene reacts with an electrophile and forms a carbocation intermediate (Section 6.0). In the second step of the reaction, the carbocation reacts with a nucleophile (Z^-) to form an addition product.

$$RCH{=}CHR + Y^+ \rightleftharpoons R\overset{+}{C}H{-}CHR(Y) \xrightarrow{Z^-} RCH(Z){-}CHR(Y)$$

carbocation intermediate

product of electrophilic addition

If the carbocation intermediate that is formed from the reaction of benzene with an electrophile were to react similarly with a nucleophile (depicted as path *a* in Figure 7.4), then the *addition product* would not be aromatic. But, if the carbocation instead were to lose a proton from the site of electrophilic addition and form a *substitution product* (depicted as path *b* in Figure 7.4), then the aromaticity of the benzene ring would be restored.

Because the aromatic substitution product is much more stable than the nonaromatic addition product (Figure 7.5), benzene undergoes *electrophilic substitution reactions* that preserve aromaticity, rather than *electrophilic addition reactions*—the reactions characteristic of alkenes—that would destroy aromaticity. The substitution reaction is more accurately called an **electrophilic aromatic substitution reaction,** since the electrophile substitutes for a hydrogen of an aromatic compound.

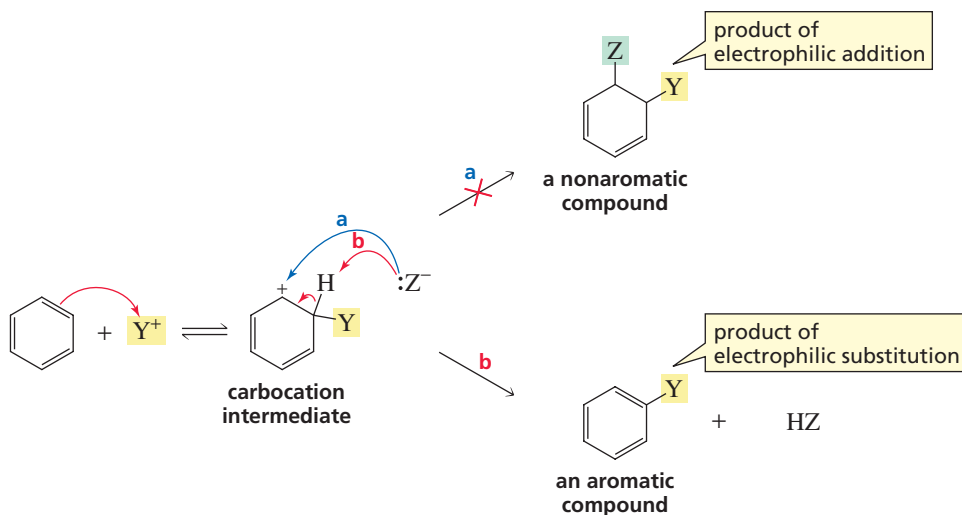
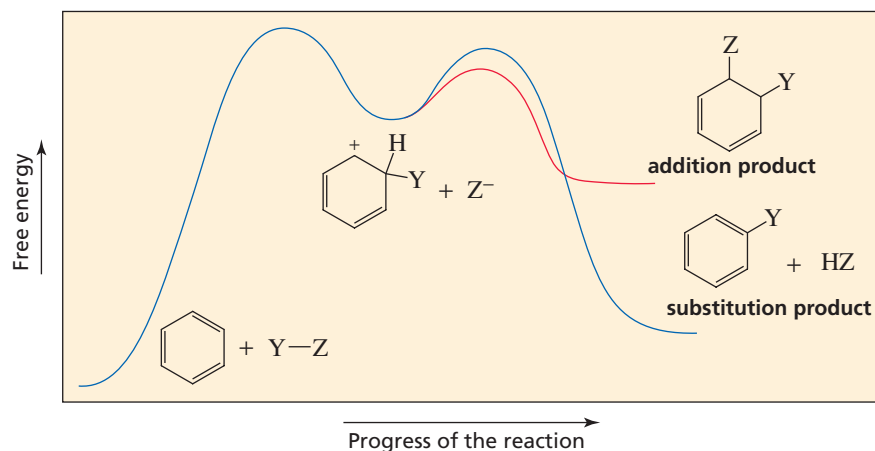
product of electrophilic addition

a nonaromatic compound

carbocation intermediate

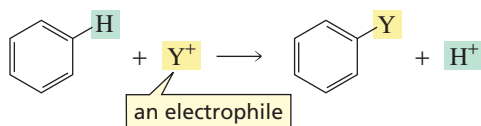
product of electrophilic substitution

+ HZ

an aromatic compound

▲ **Figure 7.4**
Reaction of benzene with an electrophile. Because of the greater stability of the aromatic product, the reaction proceeds by an electrophilic substitution reaction (path *b*) rather than by an electrophilic addition reaction (path *a*).

▲ **Figure 7.5**
Reaction coordinate diagrams for electrophilic aromatic substitution and electrophilic addition.

7.17 THE MECHANISM FOR ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

In an electrophilic aromatic substitution reaction, an electrophile becomes attached to a ring carbon and an H^+ is removed from the same ring carbon.

an electrophilic aromatic substitution reaction

Y^+ (an electrophile) $\longrightarrow$ + H^+

The Five Most Common Electrophilic Aromatic Substitution Reactions

1. **Halogenation:** A bromine (Br), a chlorine (Cl), or an iodine (I) substitutes for a hydrogen.
2. **Nitration:** A nitro group (NO_2) substitutes for a hydrogen.

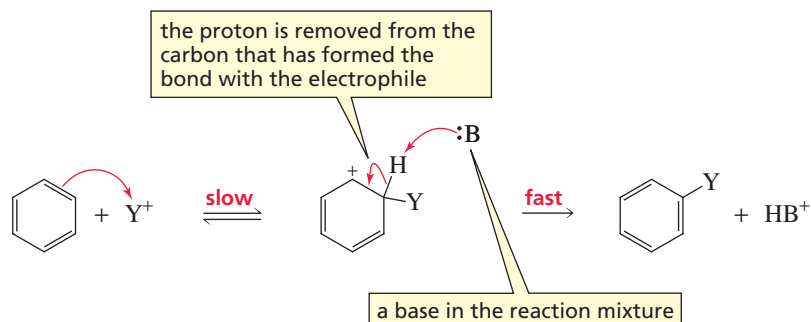
3. **Sulfonation:** A sulfonic acid group (SO_3H) substitutes for a hydrogen.
4. **Friedel–Crafts acylation:** An acyl group (RC=O) substitutes for a hydrogen.
5. **Friedel–Crafts alkylation:** An alkyl group (R) substitutes for a hydrogen.

All five of these reactions take place by the same two-step mechanism.

MECHANISM FOR ELECTROPHILIC AROMATIC SUBSTITUTION

the proton is removed from the carbon that has formed the bond with the electrophile

benzene + Y^+ $\xrightarrow{\text{slow}}$ (carbocation intermediate with H and Y; :B removes H) $\xrightarrow{\text{fast}}$ substituted benzene (Y) + HB^+

a base in the reaction mixture

- The electrophile (Y^+) adds to the nucleophilic benzene ring, thereby forming a carbocation intermediate.
- A base in the reaction mixture (:B) removes a proton from the carbocation intermediate, and the electrons that held the proton move into the ring to reestablish its aromaticity. Notice that *the proton is always removed from the carbon that has formed the bond with the electrophile.*

The first step is relatively slow and endergonic because an aromatic compound is being converted into a much less stable nonaromatic intermediate (Figure 7.5). The second step is fast and strongly exergonic because this step restores the stability-enhancing aromaticity.

The only difference in the five electrophilic aromatic substitution reactions listed above is the way in which the electrophile (Y^+) that is needed to start the reaction is generated. Once the electrophile is formed, all five reactions follow the same two-step mechanism for electrophilic aromatic substitution that was just shown.

Generation of the Electrophile

1. Halogenation:

$$:\ddot{Br}-\ddot{Br}: + FeBr_3 \longrightarrow :\ddot{Br}-\overset{+}{\ddot{Br}}-\overset{-}{F}eBr_3 \longrightarrow Br^+ + \overset{-}{F}eBr_4$$

the electrophile needed for bromination

nitric acid

2. Nitration:

$$H\ddot{O}-NO_2 + H-OSO_3H \rightleftharpoons H\overset{H}{\ddot{O}^+}-NO_2 \rightleftharpoons {}^+NO_2 + H_2\ddot{O}:$$

nitric acid — nitronium ion

$+ \ HSO_4^-$

the electrophile needed for nitration

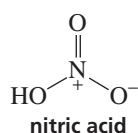
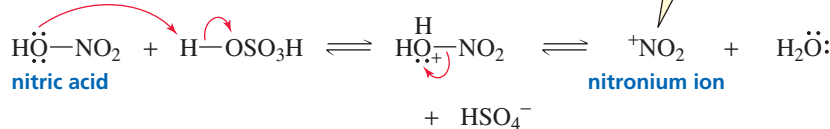
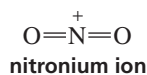
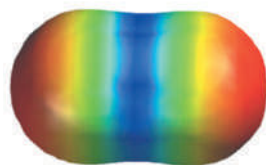
$O=\overset{+}{N}=O$

nitronium ion

3. Sulfonation:

$$H\ddot{O}-SO_3H + H-OSO_3H \rightleftharpoons H\overset{H}{\ddot{O}^+}-SO_3H \rightleftharpoons {}^+SO_3H + H_2\ddot{O}: \rightleftharpoons SO_3 + H_3O^+$$

sulfuric acid — sulfonium ion

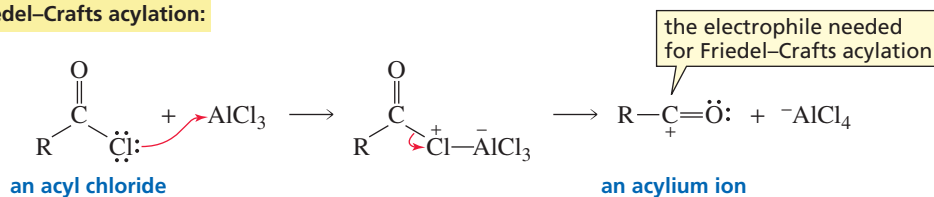
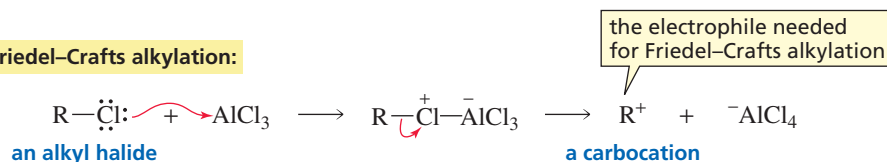
$+ \ HSO_4^-$

the electrophile needed for sulfonation

4. Friedel–Crafts acylation:

$$RC(=O)\ddot{Cl}: + AlCl_3 \longrightarrow RC(=O)\overset{+}{Cl}-\overset{-}{Al}Cl_3 \longrightarrow R-\overset{+}{C}=\ddot{O}: + {}^-AlCl_4$$

an acyl chloride — an acylium ion (the electrophile needed for Friedel–Crafts acylation)

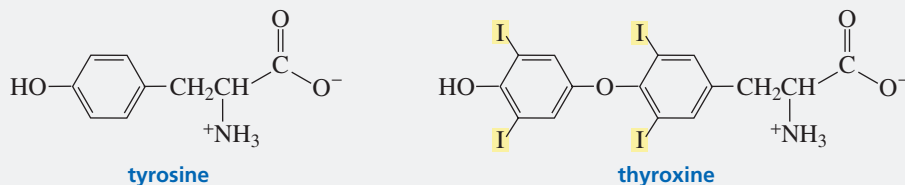
5. Friedel–Crafts alkylation:

$$R-\ddot{Cl}: + AlCl_3 \longrightarrow R-\overset{+}{Cl}-\overset{-}{Al}Cl_3 \longrightarrow R^+ + {}^-AlCl_4$$

an alkyl halide — a carbocation (the electrophile needed for Friedel–Crafts alkylation)

Thyroxine

Thyroxine, a hormone produced by the thyroid gland, increases the rate at which fats, carbohydrates, and proteins are metabolized. Humans obtain thyroxine from tyrosine (an amino acid) and iodine. The thyroid gland is the only part of the body that uses iodine, which we acquire primarily from seafood or iodized salt.

An enzyme called iodoperoxidase converts the I^- that we ingest to I^+, the electrophile needed to place an iodo substituent on a benzene ring. A deficiency in iodine is the number one cause of preventable intellectual disability in children.

$HO-C_6H_4-CH_2CH(^+NH_3)-C(=O)O^-$ — tyrosine

$HO-C_6H_2I_2-O-C_6H_2I_2-CH_2CH(^+NH_3)-C(=O)O^-$ — thyroxine

Chronically low levels of thyroxine cause enlargement of the thyroid gland as it tries in vain to make more thyroxine, a condition known as goiter. Low thyroxine levels can be corrected by taking thyroxine orally. Synthroid, the most popular brand of thyroxine, is currently one of the most-prescribed drugs in the United States.

PROBLEM 28 Solved

Propose a mechanism for the following reaction:

$$C_6H_6 \xrightarrow{DCl} C_6D_6$$

Solution The only electrophile available is D^+. Therefore, D^+ adds to a ring carbon and a base removes a proton from the same ring carbon. The reaction can be repeated at each of the other five ring carbons.

$$C_6H_6 + D^+ \rightleftharpoons [C_6H_6D]^+ \xrightarrow{:B} C_6H_5D + H^+$$

PROBLEM 29

Draw the mechanism for the reaction of benzene with the following electrophiles to form a substituted benzene:

a. ^{+}Br

b. $^{+}NO_2$

c. $CH_3\overset{+}{C}{=}O$

d. $(CH_3)_3C^+$

PROBLEM 30

What would be the major product of a Friedel–Crafts alkylation using the following alkyl chlorides?

a. CH_3CH_2Cl **b.** $CH_3CH_2CH(Cl)CH_3$ **c.** $(CH_3)_3CCl$ **d.** $CH_2{=}CHCH_2Cl$

7.18 ORGANIZING WHAT WE KNOW ABOUT THE REACTIONS OF ORGANIC COMPOUNDS

When you were first introduced to the reactions of organic compounds in Section 5.2, you saw that organic compounds can be classified into families and that all the members of a family react in the same way. You also saw that each family can be put into one of four groups, and that all the families in a group react in similar ways. Let's revisit the first group.

All the families in the first group are nucleophiles, because of their electron-rich carbon–carbon double or triple bonds. And because double and triple bonds have relatively weak π bonds, the families in this group undergo addition reactions. Since the first species that reacts with a nucleophile is an electrophile, the reactions that the families in this group undergo are more precisely called *electrophilic addition reactions.*

- Alkenes have one π bond, so they undergo one electrophilic addition reaction.
- Alkynes have two π bonds, so they can undergo two electrophilic addition reactions. However, if the first addition reaction forms an enol, the enol immediately rearranges to a ketone (or to an aldehyde), so a second addition reaction cannot occur.
- If the double bonds of a diene are isolated, they react just like alkenes. If, however, the double bonds are conjugated, they undergo both 1,2- and 1,4-addition reactions, because the carbocation intermediate has delocalized electrons.

Benzene belongs to the second group. Benzene is a nucleophile, so the first species it reacts with is an electrophile. To preserve its aromaticity, benzene undergoes electrophilic aromatic substitution reactions.

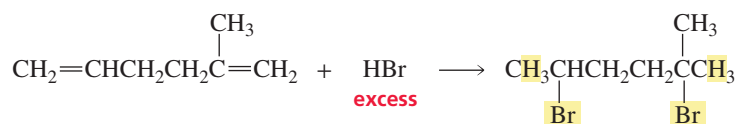
In Chapter 8, we will move on to the families in the third group.

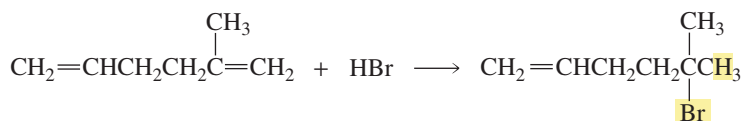
SOME IMPORTANT THINGS TO REMEMBER

- **Localized electrons** belong to a single atom or are shared by two atoms. **Delocalized electrons** are shared by more than two atoms.
- Delocalized electrons result when a *p* orbital overlaps the *p* orbitals of two adjacent atoms.
- Electron delocalization occurs only if all the atoms sharing the delocalized electrons lie in or close to the same plane.
- The six π electrons of benzene are shared by all six carbons. Thus, benzene is a planar molecule with six delocalized π electrons.
- **Resonance contributors**—structures with localized electrons—approximate the structure of a compound that has delocalized electrons: the **resonance hybrid.**
- To draw resonance contributors, move π electrons or lone-pair electrons toward an sp^2 atom.
- The greater the predicted stability of the resonance contributor, the more it contributes to the structure of the hybrid, and the more similar its structure is to the real molecule.
- **A resonance hybrid** is more stable than the predicted stability of any of its resonance contributors.
- **Delocalization energy** (or **resonance energy**) is the extra stability a compound gains from having delocalized electrons. It tells us how much more stable a compound with delocalized electrons is than it would be if all its electrons were localized.
- The greater the number of relatively stable resonance contributors and the more nearly equivalent they are, the greater the delocalization energy.
- A carboxylic acid and a phenol are more acidic than an alcohol, and a protonated aniline is more acidic than a protonated amine because *loss of a proton from a carboxylic acid, a phenol, or a protonated aniline* is accompanied by *an increase in delocalization energy.*
- Donation of electrons through π bonds is called **resonance electron donation;** withdrawal of electrons through π bonds is called **resonance electron withdrawal.**
- Substituents attached to benzene rings can withdraw electrons **inductively,** donate electrons by **hyperconjugation,** and withdraw and donate electrons by **resonance.**
- Electron-withdrawing substituents increase the acidity (decrease the pK_a values) of substituted phenols, benzoic acids, and protonated anilines, whereas electron-donating substituents decrease their acidity (increase the pK_a values).
- An isolated diene, like an alkene, undergoes only 1,2-addition. If there is only enough electrophilic reagent to add to one of the double bonds, it will add preferentially to the one that forms the more stable carbocation.
- A conjugated diene reacts with one equivalent of an electrophilic reagent to form a **1,2-addition product** and a **1,4-addition product.** The first step is addition of the electrophile to one of the sp^2 carbons at the end of the conjugated system.
- In a **Diels–Alder reaction,** a **conjugated diene** reacts with a **dienophile** to form a cyclic compound.
- The reactivity of the **dienophile** is increased by electron-withdrawing groups attached to an sp^2 carbon.
- An **aromatic compound** has an uninterrupted cyclic cloud of π electrons that contains an *odd number of pairs* of π electrons. Aromatic compounds are very stable.
- Benzene is aromatic, so it undergoes **electrophilic aromatic substitution reactions.**
- The most common electrophilic aromatic substitution reactions are halogenation, nitration, sulfonation, and Friedel–Crafts acylation and alkylation.
- Once the electrophile is generated, all electrophilic aromatic substitution reactions take place by the same two-step mechanism: (1) benzene forms a bond with the electrophile, forming a carbocation intermediate; and (2) a base removes a proton from the carbon that formed the bond with the electrophile.

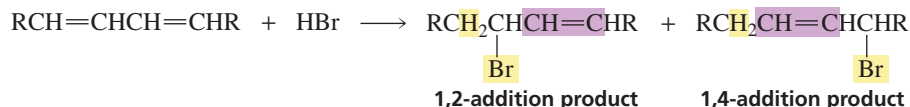
SUMMARY OF REACTIONS

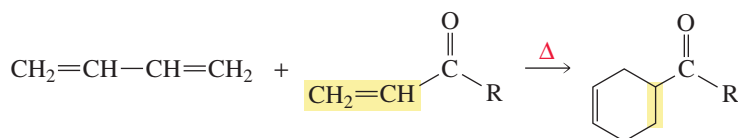
1. In the presence of excess electrophilic reagent, both double bonds of an *isolated diene* will undergo electrophilic addition (Section 7.11). The mechanism is on page 264.

$$CH_2{=}CHCH_2CH_2\overset{\overset{\large CH_3}{|}}{C}{=}CH_2 \; + \; \underset{\text{excess}}{HBr} \longrightarrow CH_3\underset{\underset{\large Br}{|}}{C}HCH_2CH_2\underset{\underset{\large Br}{|}}{\overset{\overset{\large CH_3}{|}}{C}}CH_3$$

In the presence of just one equivalent of electrophilic reagent, only the most reactive double bond of an *isolated diene* will undergo electrophilic addition.

$$CH_2{=}CHCH_2CH_2\underset{}{\overset{CH_3}{\overset{|}{C}}}{=}CH_2 + HBr \longrightarrow CH_2{=}CHCH_2CH_2\underset{Br}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_3$$

2. Conjugated dienes undergo 1,2- and 1,4-addition in the presence of one equivalent of an electrophilic reagent (Section 7.11). The mechanism is on page 265.

$$RCH{=}CHCH{=}CHR + HBr \longrightarrow RCH_2\underset{Br}{\underset{|}{C}}HCH{=}CHR + RCH_2CH{=}CH\underset{Br}{\underset{|}{C}}HR$$

1,2-addition product **1,4-addition product**

3. Conjugated dienes undergo 1,4-addition with a dienophile (the Diels–Alder reaction; see Section 7.12). The mechanism is on page 266.

$$CH_2{=}CH{-}CH{=}CH_2 + CH_2{=}CH\overset{O}{\overset{\|}{C}}R \xrightarrow{\Delta} \text{cyclohexene}{-}\overset{O}{\overset{\|}{C}}R$$

4. Electrophilic aromatic substitution reactions (Sections 17.16 and 17.17). The mechanisms are shown on page 274.

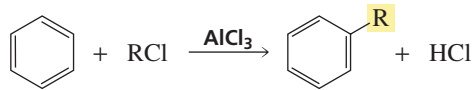
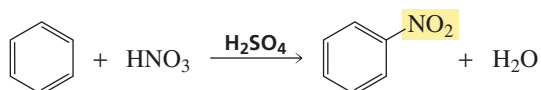
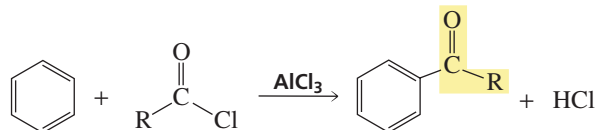
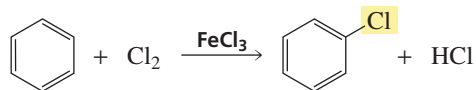
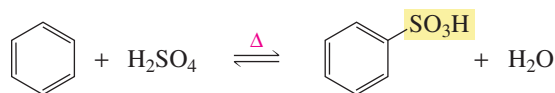
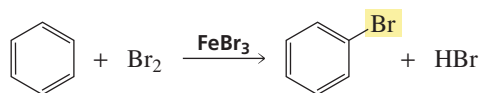
$$C_6H_6 + Br_2 \xrightarrow{FeBr_3} C_6H_5Br + HBr$$

$$C_6H_6 + H_2SO_4 \overset{\Delta}{\rightleftharpoons} C_6H_5SO_3H + H_2O$$

$$C_6H_6 + Cl_2 \xrightarrow{FeCl_3} C_6H_5Cl + HCl$$

$$C_6H_6 + R\overset{O}{\overset{\|}{C}}Cl \xrightarrow{AlCl_3} C_6H_5\overset{O}{\overset{\|}{C}}R + HCl$$

$$C_6H_6 + HNO_3 \xrightarrow{H_2SO_4} C_6H_5NO_2 + H_2O$$

$$C_6H_6 + RCl \xrightarrow{AlCl_3} C_6H_5R + HCl$$

PROBLEMS

31. Which of the following have delocalized electrons?

a. $CH_2{=}CH\overset{O}{\overset{\|}{C}}CH_3$

b. $CH_3CH{=}CHOCH_2CH_3$

c. $CH_3CH{=}CHCH{=}CH\overset{+}{C}H_2$

d. $CH_3\overset{+}{C}HCH_2CH{=}CH_2$

e. cyclopentene cation (+ on ring carbon not adjacent to the double bond)

f. $CH_3\underset{+}{\overset{CH_3}{\overset{|}{C}}}CH_2CH{=}CH_2$

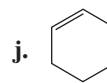
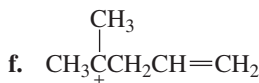
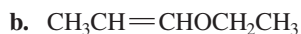
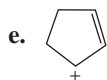
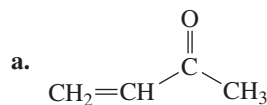
g. $CH_2{=}CHCH_2CH{=}CH_2$

h. $CH_3CH_2NHCH_2CH{=}CHCH_3$

i. cyclopentene cation (+ on ring carbon)

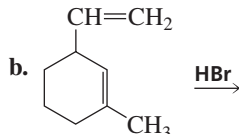
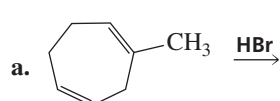
j. 1,3-cyclohexadiene

k. $CH_3CH_2\overset{+}{C}HCH{=}CH_2$

l. $CH_3CH_2NHCH{=}CHCH_3$

32. What is the major product of each of the following reactions? Assume that there is an equivalent amount of each reagent.

a. 1-methylcycloheptadiene (CH_3 substituent) $\xrightarrow{HBr}$

b. cyclohexene ring bearing $CH{=}CH_2$ and CH_3 substituents $\xrightarrow{HBr}$

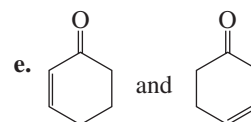
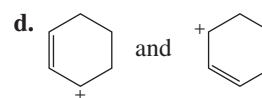
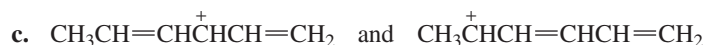
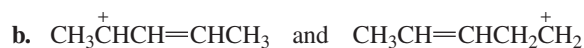
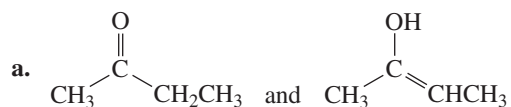
c. $C_6H_5{-}CH{=}CH_2 + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow{\Delta}$

33. Are the following pairs of structures resonance contributors or different compounds?

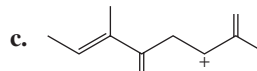
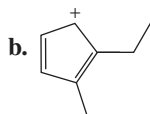
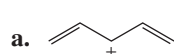
a.

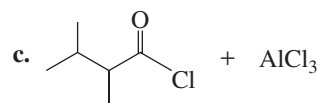
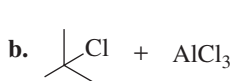
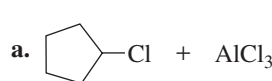
b. $CH_3\overset{+}{C}HCH{=}CHCH_3$ and $CH_3CH{=}CHCH_2\overset{+}{C}H_2$

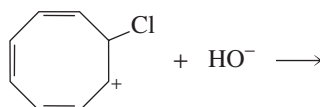
c. $CH_3CH{=}CH\overset{+}{C}HCH{=}CH_2$ and $CH_3\overset{+}{C}HCH{=}CHCH{=}CH_2$

d. and

e.

34. Draw resonance contributors for the following carbocations:

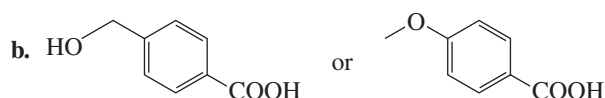
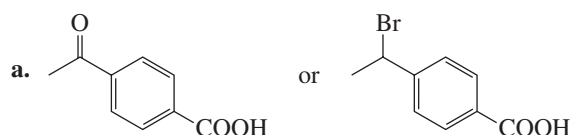
a. **b.** **c.**

35. What product is formed when benzene reacts with each of the following reagents?

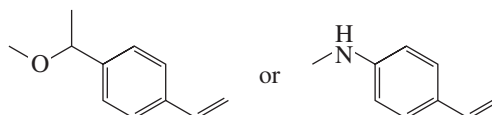
a. Cl + $AlCl_3$ **b.** Cl + $AlCl_3$ **c.** O Cl + $AlCl_3$

36. Draw all the products of the following reaction:

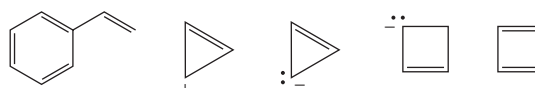
Cl + HO^- ⟶

37. For each of the statements in Column I, choose a substituent from Column II that fits the description for a substituent (Z) attached to a benzene ring:

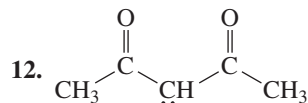
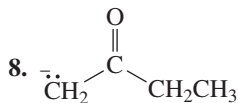
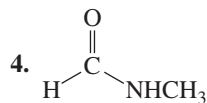
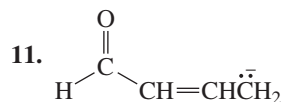
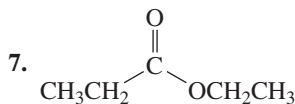
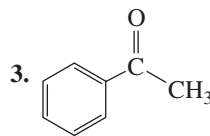
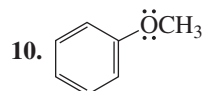
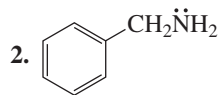
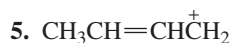
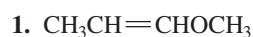
	Column I	Column II
a.	Z donates electrons inductively, but does not donate or withdraw electrons by resonance.	OH
b.	Z withdraws electrons inductively and withdraws electrons by resonance.	Br
c.	Z withdraws electrons inductively and donates electrons by resonance, but is better at withdrawing inductively.	$^+NH_3$
d.	Z withdraws electrons inductively and donates electrons by resonance, but is better at donating by resonance.	CH_2CH_3
e.	Z withdraws electrons inductively, but does not donate or withdraw electrons by resonance.	NO_2

38. Which of the compounds in each of the following pairs is more acidic?

a. COOH or Br COOH **b.** HO COOH or O COOH

39. Which of the following compounds will react with HBr more rapidly?

O or H N

40. Which compound would you expect to have the greater heat of hydrogenation, 1,2-pentadiene or 1,4-pentadiene?

41. Which of the following species are aromatic?

42. a. Draw resonance contributors for the following species. Indicate which are major contributors and which are minor contributors to the resonance hybrid.

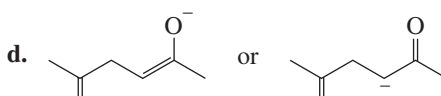
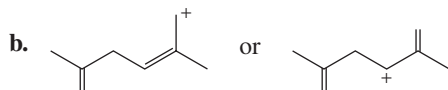
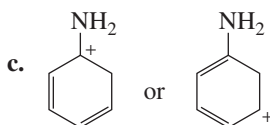
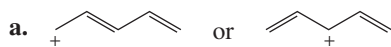
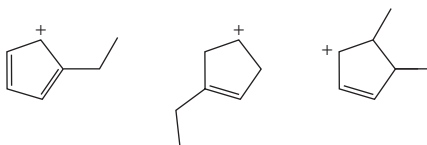
1. $CH_3CH{=}CHOCH_3$
2. (benzene)–$CH_2\ddot{N}H_2$
3. (benzene)–C(=O)–CH_3
4. H–C(=O)–$NHCH_3$
5. $CH_3CH{=}CH\overset{+}{C}H_2$
6. (cyclopentadienyl cation, +)
7. CH_3CH_2–C(=O)–OCH_2CH_3
8. $\ddot{\bar{C}}H_2$–C(=O)–CH_2CH_3
9. $CH_3CH{=}CHCH{=}CH\overset{+}{C}H_2$
10. (benzene)–$\ddot{O}CH_3$
11. H–C(=O)–$CH{=}CH\ddot{\bar{C}}H_2$
12. CH_3–C(=O)–$\ddot{\bar{C}}H$–C(=O)–CH_3

b. Do any of the species have resonance contributors that all contribute equally to the resonance hybrid?

43. Which resonance contributor in each pair makes the greater contribution to the resonance hybrid?

a. or

b. or

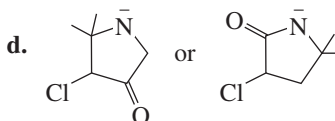
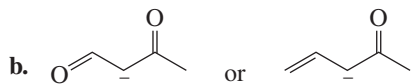
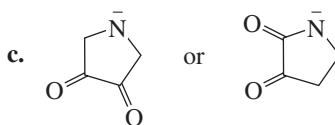
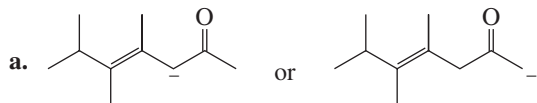
c. NH_2 or NH_2

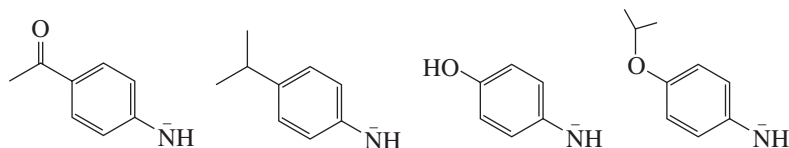
d. O^- or O

44. Rank the following carbocations in order from most stable to least stable:

45. Which species in each pair is more stable?

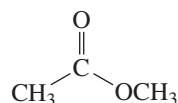
a. O or O

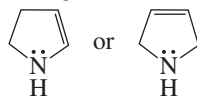
b. O O or O

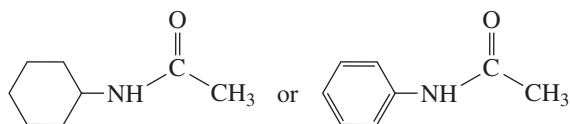
c. N O O or O N O

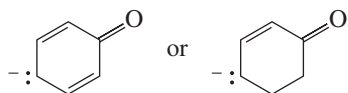
d. N Cl O or O N Cl

46. Which species in each of the pairs in Problem 45 is the stronger base?

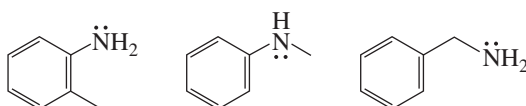
47. Rank the following anions in order from most basic to least basic:

48. a. Which oxygen atom has the greater electron density?

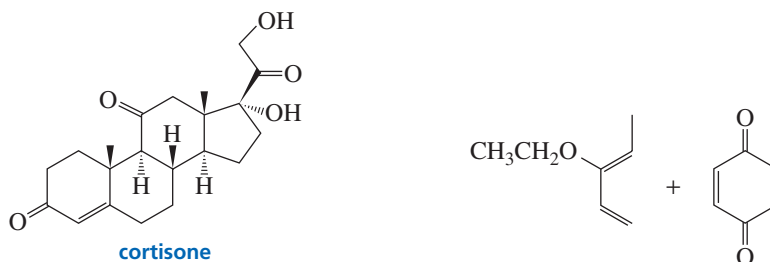
CH_3–C(=O)–OCH_3

b. Which compound has the greater electron density on its nitrogen atom?

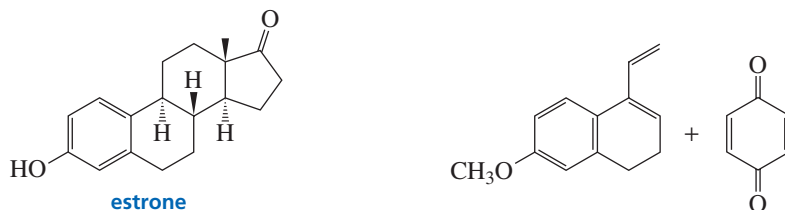
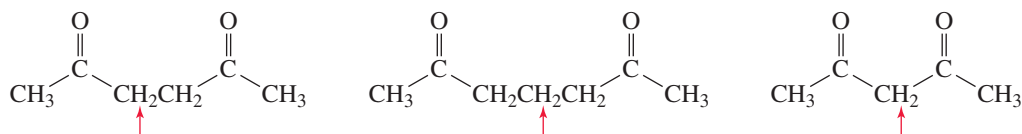
$\ddot{N}$H or $\ddot{N}$H

c. Which compound has the greater electron density on its oxygen atom?

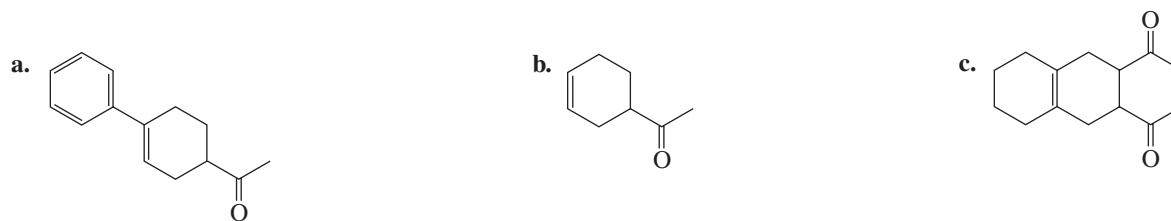
or

d. Which species is a stronger base?

or

49. Which can lose a proton more readily, a methyl group bonded to cyclohexane or a methyl group bonded to benzene?

50. Which compound is the strongest base?

51. a. The B ring of cortisone (Section 3.14), a steroid, is formed by a Diels–Alder reaction using the two reactants shown here. What is the product of this reaction?

cortisone

b. The C ring of estrone (a steroid) is formed by a Diels–Alder reaction using the two reactants shown here. What is the product of this reaction?

estrone

52. Rank the indicated hydrogen in the following compounds in order from most acidic to least acidic:

53. How could the following compounds be synthesized using a Diels–Alder reaction?

a. **b.** **c.**

54. Draw the products obtained from the reaction of 1 equivalent of HBr with 1 equivalent of 2,5-dimethyl-1,3,5-hexatriene.

55. How would the following substituents affect the rate of a Diels–Alder reaction?

a. an electron-donating substituent in the diene
b. an electron-donating substituent in the dienophile
c. an electron-withdrawing substituent in the diene

56. a. Which dienophile in each pair is more reactive in a Diels–Alder reaction?

1. $CH_2{=}CH\overset{O}{\overset{\|}{C}}H$ or $CH_2{=}CHCH_2\overset{O}{\overset{\|}{C}}H$ **2.** $CH_2{=}CH\overset{O}{\overset{\|}{C}}H$ or $CH_2{=}CHCH_3$

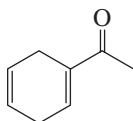
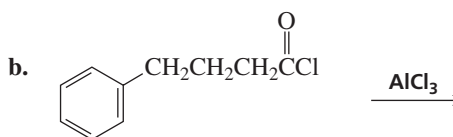
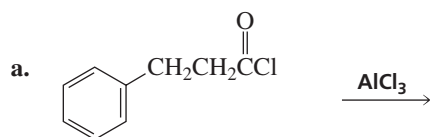
b. Which diene is more reactive in a Diels–Alder reaction?

$CH_2{=}CHCH{=}CHOCH_3$ or $CH_2{=}CHCH{=}CHCH_2OCH_3$

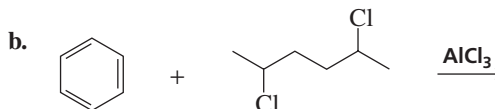
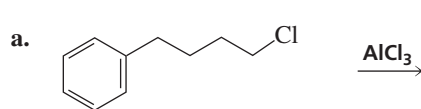
57. What two sets of a conjugated diene and a dienophile could be used to prepare the following compound?

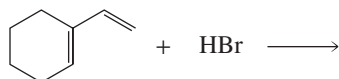
58. Draw the product of each of the following reactions:

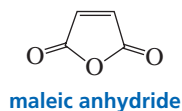
a. $C_6H_5CH_2CH_2\overset{O}{\overset{\|}{C}}Cl \xrightarrow{AlCl_3}$

b. $C_6H_5CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}Cl \xrightarrow{AlCl_3}$

59. Draw the product of each of the following reactions:

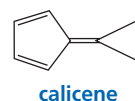
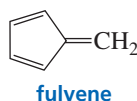
a. Cl $\xrightarrow{AlCl_3}$

b. + Cl Cl $\xrightarrow{AlCl_3}$

60. What are the products of the following and how many stereoisomers of each product could be obtained?

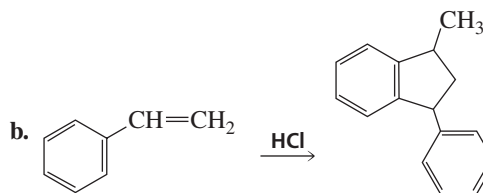
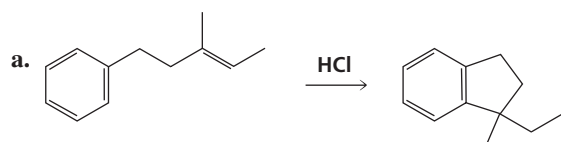
+ HBr ⟶

61. While attempting to recrystallize maleic anhydride, a student dissolved it in freshly distilled cyclopentadiene rather than in freshly distilled cyclopentane. Was his recrystallization successful?

maleic anhydride

62. a. In what direction is the dipole moment in fulvene? Explain.
b. In what direction is the dipole moment in calicene? Explain.

$=CH_2$

fulvene calicene

63. Propose a mechanism for each of the following reactions:

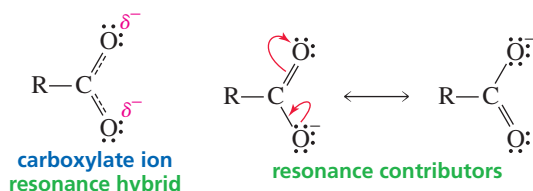
a. $\xrightarrow{HCl}$

b. $C_6H_5CH{=}CH_2 \xrightarrow{HCl}$ CH_3

DRAWING RESONANCE CONTRIBUTORS

We have seen that chemists use curved arrows to show how electrons move when reactants are converted into products (see the Tutorial on page 202). Chemists also use curved arrows when they draw resonance contributors.

We have also seen that delocalized electrons are electrons that are shared by more than two atoms. When electrons are shared by more than two atoms, we cannot use solid lines to represent the location of the electrons accurately. For example, in the carboxylate ion, a pair of electrons is shared by a carbon and two oxygens. We show the pair of delocalized electrons by a dotted line spread over the three atoms. We have seen that this structure is called a **resonance hybrid.** The resonance hybrid shows that the negative charge is shared by the two oxygens.

carboxylate ion
resonance hybrid

resonance contributors

Chemists do not like to use dotted lines when drawing structures because, unlike a solid line that represents two electrons, the dotted lines do not specify the number of electrons they represent. Therefore, chemists use structures with localized electrons (indicated by solid lines) to approximate the resonance hybrid that has delocalized electrons (indicated by dotted lines). These approximate structures are called **resonance contributors.** Curved arrows are used to show the movement of electrons in going from one resonance contributor to the next.

RULES FOR DRAWING RESONANCE CONTRIBUTORS

Now we will look at three simple rules for interconverting resonance contributors:

1. Only electrons move; atoms *never* move.
2. The only electrons that can move are π electrons (electrons in π bonds) and lone-pair electrons.
3. Electrons are always moved toward an sp^2 or sp hybridized atom. An sp^2 carbon is a positively charged carbon or a double-bonded carbon; an sp carbon is a triply bonded carbon.

(In Chapter 14, we will see that electrons can also move toward a carbon with an unpaired electron, which is an sp^2 carbon as well.)

Moving π Electrons Toward an sp^2 Carbon That Is a Positively Charged Carbon

In the following example, π electrons are moved toward a positively-charged carbon. Because the atom does not have a complete octet of electrons, it can accept the electrons. The carbon that is positively charged in the first resonance contributor is neutral in the second resonance contributor because it has received electrons. The carbon in the first resonance contributor that loses its share of the π electrons is positively charged in the second resonance contributor.

$$CH_3CH{=}CH{-}\overset{+}{C}HCH_3 \longleftrightarrow CH_3\overset{+}{C}H{-}CH{=}CHCH_3$$

We see that the following carbocation has three resonance contributors.

$$CH_2{=}CH{-}CH{=}CH{-}\overset{+}{C}HCH_3 \longleftrightarrow CH_2{=}CH{-}\overset{+}{C}H{-}CH{=}CHCH_3 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}CH{=}CHCH_3$$

Notice that in going from one resonance contributor to the next, the total number of electrons in the structure does not change. Therefore, each of the resonance contributors must have the same net charge.

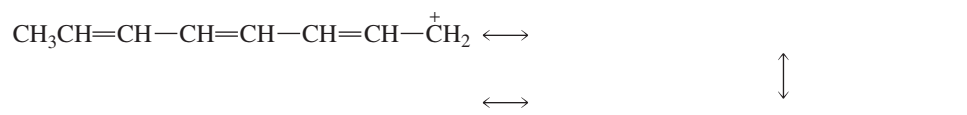
PROBLEM 1 Draw the resonance contributors for the following carbocation (the answers can be found immediately after Problem 12):

$CH_3CH{=}CH{-}CH{=}CH{-}CH{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow$

$\longleftrightarrow$

PROBLEM 2 Draw the resonance contributors for the following carbocation:

(benzyl cation: benzene ring–$\overset{+}{C}H_2$) $\longleftrightarrow \quad \longleftrightarrow \quad \longleftrightarrow \quad \longleftrightarrow$

Moving π Electrons Toward an sp^2 Carbon That Is a Doubly Bonded Carbon

In the following example, π electrons are moved toward a doubly bonded carbon. The atom to which the electrons are moved can accept them because the π bond can break.

(benzene with curved arrows) $\longleftrightarrow$ (benzene)

PROBLEM 3 Draw the resonance contributor for the following compound:

(toluene: benzene ring–CH_3) $\longleftrightarrow$

In the next example, the electrons can be moved equally easily to the left (indicated by the red arrows) or to the right (indicated by the blue arrows). When comparing the charges on the resonance contributors, we see that the charges on each of the end carbons cancel, so there is no charge on any of the carbons in the resonance hybrid.

$\overset{-}{\ddot{C}}H_2{-}CH{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow CH_2{=}CH{-}CH{=}CH_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}\overset{-}{\ddot{C}}H_2$

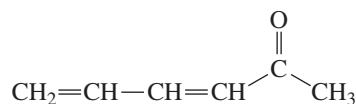
$CH_2{\overset{...}{=}}CH{\overset{...}{=}}CH{\overset{...}{=}}CH_2$

resonance hybrid

When electrons can be moved in either of two directions and there is a difference in the electronegativity of the atoms to which they can be moved, always move the electrons toward the more electronegative atom. For instance, in the following example, the electrons are moved toward oxygen, not toward carbon.

$CH_3{-}C({=}\ddot{O}{:}){-}CH{=}CH_2 \longleftrightarrow CH_3{-}C({-}{:}\ddot{O}{:}^-){=}CH{-}\overset{+}{C}H_2$

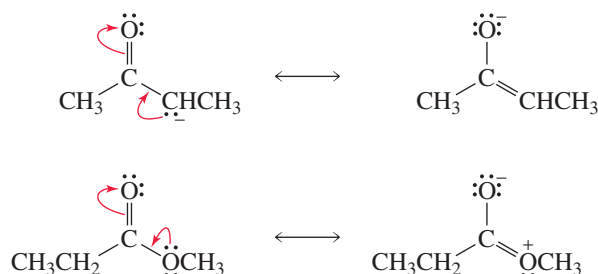
Notice that the first resonance contributor has a charge of 0. Since the number of electrons in the molecule does not change, the other resonance contributor must have a net charge of 0. (A net charge of 0 does not mean that there is no charge on any of the atoms; a resonance contributor with a positive charge on one atom and a negative charge on another has a net charge of 0.)

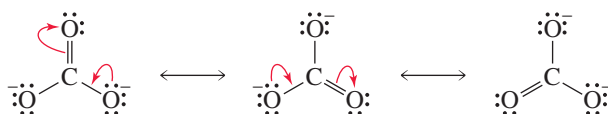
PROBLEM 4 Draw the resonance contributor for the following compound:

$$CH_2{=}CH{-}CH{=}CH{-}C({=}O){-}CH_3$$

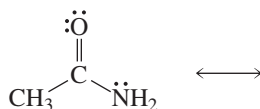
Moving a Lone Pair Toward an *sp*² Carbon That Is a Doubly Bonded Carbon

In the following examples, lone-pair electrons are moved toward a doubly bonded carbon. Notice that the arrow starts at a pair of electrons, not at a negative charge. In the first example, each of the resonance contributors has a charge of −1; in the second example, each of the resonance contributors has no charge or net charge of 0.

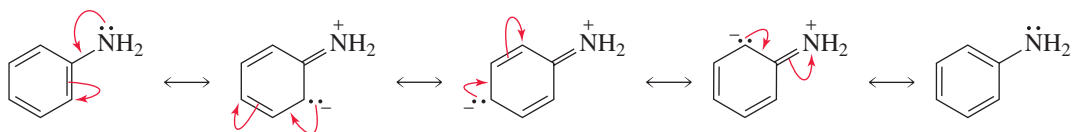
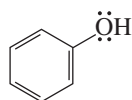
$$CH_3C({=}\ddot{O}{:}){\ddot{C}}^{-}HCH_3 \longleftrightarrow CH_3C({-}{:}\ddot{O}{:}^{-}){=}CHCH_3$$

$$CH_3CH_2C({=}\ddot{O}{:}){-}\ddot{O}CH_3 \longleftrightarrow CH_3CH_2C({-}{:}\ddot{O}{:}^{-}){=}\overset{+}{\ddot{O}}CH_3$$

The following species has three resonance contributors. Notice again that the arrow starts at a lone pair, not at a negative charge. The three oxygen atoms share the two negative charges. Therefore, each oxygen atom in the hybrid has two-thirds of a negative charge.

$$^{-}{:}\ddot{O}{-}C({=}\ddot{O}{:}){-}\ddot{O}{:}^{-} \longleftrightarrow {}^{-}{:}\ddot{O}{-}C({-}{:}\ddot{O}{:}^{-}){=}\ddot{O}{:} \longleftrightarrow {:}\ddot{O}{=}C({-}{:}\ddot{O}{:}^{-}){-}\ddot{O}{:}^{-}$$

PROBLEM 5 Draw the resonance contributor for the following compound:

$$CH_3C({=}\ddot{O}{:}){-}\ddot{N}H_2 \longleftrightarrow$$

Notice in the next example that the lone pair of electrons moves away from the most electronegative atom in the molecule. This is the only way electron delocalization can occur (and any electron delocalization is better than none). The π electrons cannot move toward the oxygen because the oxygen atom has a complete octet (it is sp^3 hybridized). Recall that electrons can move only toward an sp^2 or sp hybridized atom.

$$CH_3CH{=}CH{-}\ddot{O}CH_3 \longleftrightarrow CH_3\overset{-}{\ddot{C}}H{-}CH{=}\overset{+}{\ddot{O}}CH_3$$

The compound in the next example has five resonance contributors. To get to the second resonance contributor, a lone pair on nitrogen is moved toward an sp^2 carbon. Notice that the first and fifth resonance contributors are not the same; they are similar to the two resonance contributors of benzene. (See page 246.)

PROBLEM 6 Draw the resonance contributors for the following compound:

The following species do not have delocalized electrons. Electrons cannot be moved toward an sp^3 hybridized atom because an sp^3 hybridized atom has a complete octet and it does not have a π bond that can break, so it cannot accept any more electrons.

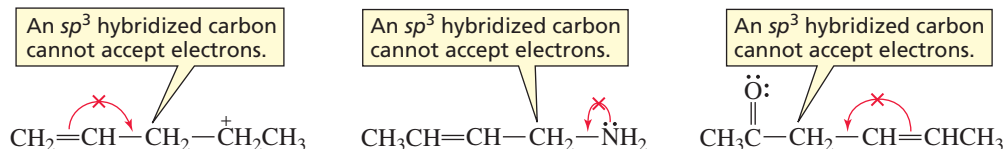
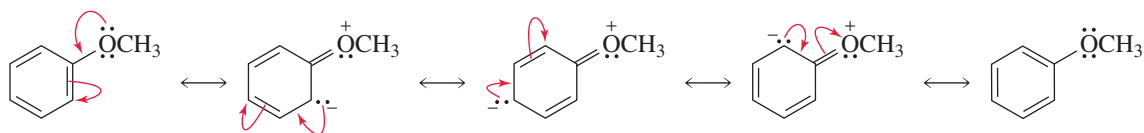
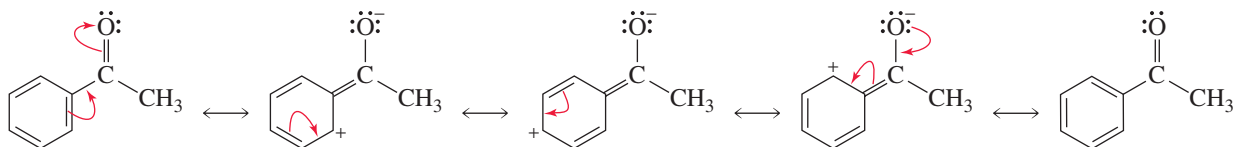
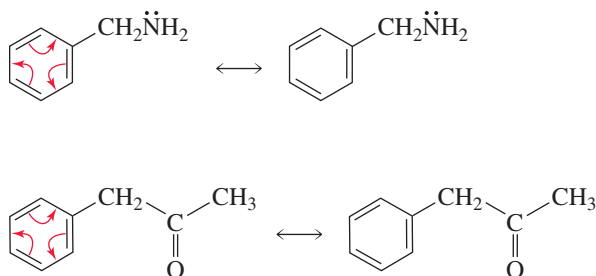
An sp^3 hybridized carbon cannot accept electrons.

$CH_2{=}CH{-}CH_2{-}\overset{+}{C}H_2CH_3$

An sp^3 hybridized carbon cannot accept electrons.

$CH_3CH{=}CH{-}CH_2{-}\ddot{N}H_2$

An sp^3 hybridized carbon cannot accept electrons.

$CH_3C(=O){-}CH_2{-}CH{=}CHCH_3$

Notice the difference in the resonance contributors for the next two examples. In the first example, electrons *move into* the benzene ring. That is, a lone pair on the atom attached to the ring moves toward an sp^2 carbon.

In the next example, electrons *move out* of the benzene ring. First, a π bond moves toward an sp^2 carbon. The electron movement is toward the oxygen since oxygen is more electronegative than carbon. Then, to draw the other resonance contributors, a π bond moves toward a positive charge.

In the next two examples, the atom attached to the ring has neither a lone pair nor a π bond. Therefore, the substituent can neither donate electrons into the ring nor accept electrons from the ring. Thus, these compounds have only two resonance contributors—the ones that are similar to the two resonance contributors of benzene.

PROBLEM 7 Which of the following species have delocalized electrons?

$CH_3CH{=}CHCH_2CH{=}CH_2$ **A**

$CH_3CH{=}CHCH{=}CH_2$ **B**

$CH_3CH{=}CHCH_2\ddot{N}HCH_3$ **C**

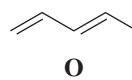
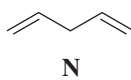
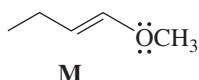
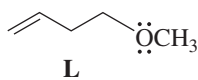
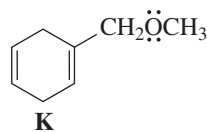
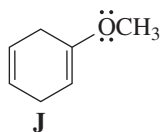
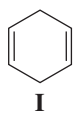
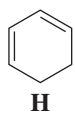
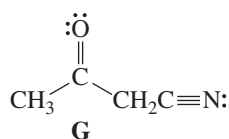
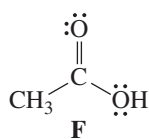
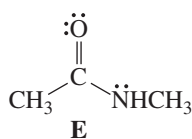
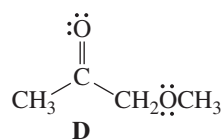
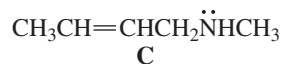
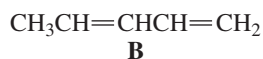
$CH_3C(=\ddot{O})CH_2\ddot{O}CH_3$ **D**

$CH_3C(=\ddot{O})\ddot{N}HCH_3$ **E**

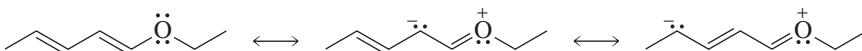
$CH_3C(=\ddot{O})\ddot{O}H$ **F**

$CH_3C(=\ddot{O})CH_2C{\equiv}N{:}$ **G**

H **I** **J** ($\ddot{O}CH_3$) **K** ($CH_2\ddot{O}CH_3$)

L ($\ddot{O}CH_3$) **M** ($\ddot{O}CH_3$) **N** **O**

PROBLEM 8 Draw the resonance contributors for those compounds in Problem 7 that have delocalized electrons.

PROBLEM 9 Draw curved arrows to show how one resonance contributor leads to the next one.

$\longleftrightarrow$ $\longleftrightarrow$

PROBLEM 10 Draw the resonance contributors for each of the following species:

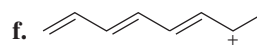
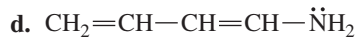
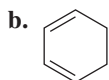
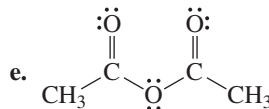
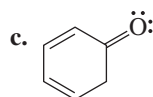
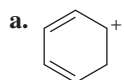
a. (+)

b.

c. ($\ddot{O}{:}$)

d. $CH_2{=}CH{-}CH{=}CH{-}\ddot{N}H_2$

e. $CH_3C(=\ddot{O})\ddot{O}C(=\ddot{O})CH_3$

f. (+)

PROBLEM 11 Draw the resonance contributors for each of the following species:

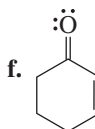
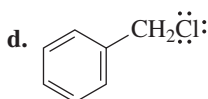
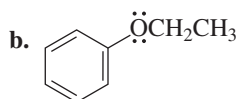
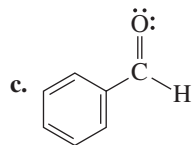
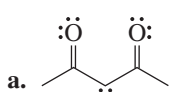
a. ($\ddot{O}$, $\ddot{O}$, $\ddot{}^{-}$)

b. ($\ddot{O}CH_2CH_3$)

c. ($C(=\ddot{O})H$)

d. ($CH_2\ddot{Cl}{:}$)

e. (+)

f. ($\ddot{O}$)

PROBLEM 12 Draw the resonance contributors for each of the following species:

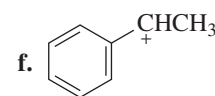
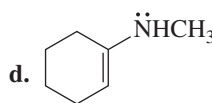
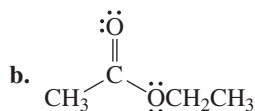
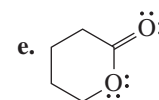
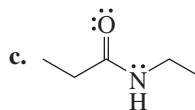
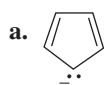
a. (cyclopentadienyl anion)

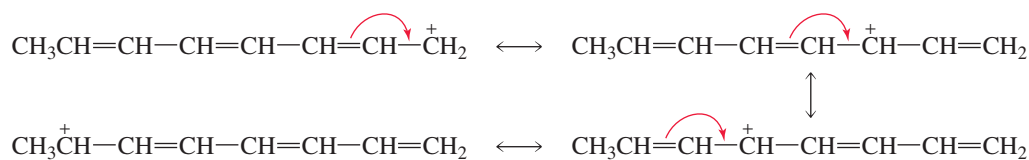
b. $CH_3C(=O)\ddot{O}CH_2CH_3$

c. (N-ethylpropanamide)

d. (1-cyclohexenyl-$\ddot{N}HCH_3$)

e. (δ-valerolactone)

f. (benzene–$\overset{+}{C}HCH_3$)

ANSWERS TO PROBLEMS ON DRAWING RESONANCE CONTRIBUTORS

PROBLEM 1 Answer

$CH_3CH{=}CH{-}CH{=}CH{-}CH{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow CH_3CH{=}CH{-}CH{=}CH{-}\overset{+}{C}H{-}CH{=}CH_2$

$\updownarrow$

$CH_3\overset{+}{C}H{-}CH{=}CH{-}CH{=}CH{-}CH{=}CH_2 \longleftrightarrow CH_3CH{=}CH{-}\overset{+}{C}H{-}CH{=}CH{-}CH{=}CH_2$

PROBLEM 2 Answer

$\overset{+}{C}H_2$ ⟷ CH_2 (+) ⟷ CH_2 (+) ⟷ CH_2 (+) ⟷ $\overset{+}{C}H_2$

PROBLEM 3 Answer

CH_3 ⟷ CH_3

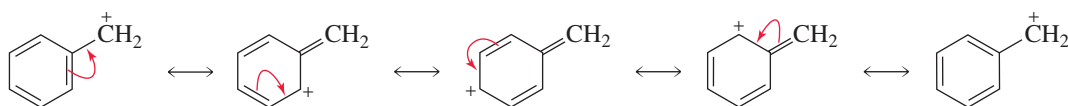
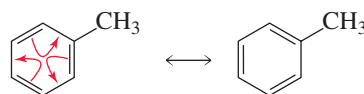
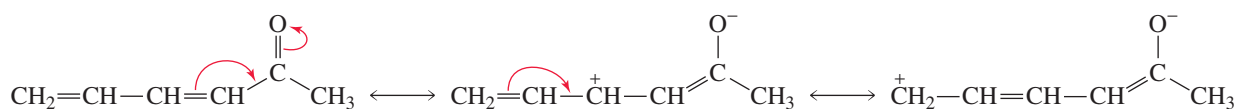
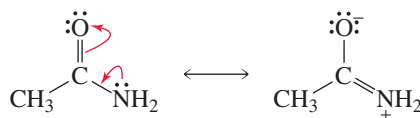
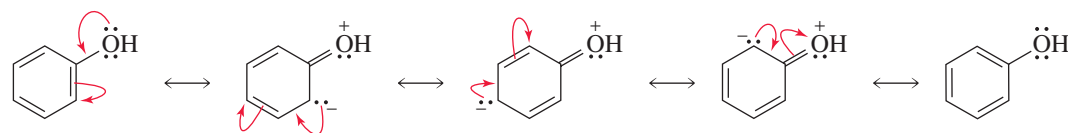
PROBLEM 4 Answer

$CH_2{=}CH{-}CH{=}CH{-}C(=O){-}CH_3 \longleftrightarrow CH_2{=}CH{-}\overset{+}{C}H{-}CH{=}C(O^-){-}CH_3 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}CH{=}C(O^-){-}CH_3$

PROBLEM 5 Answer

$CH_3C(=\ddot{O}){-}\ddot{N}H_2 \longleftrightarrow CH_3C(\ddot{O}^-){=}\overset{+}{N}H_2$

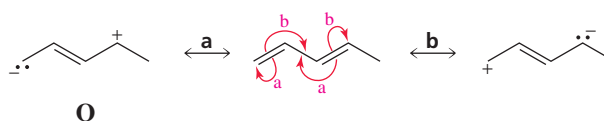
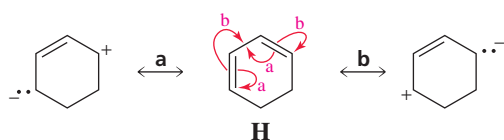
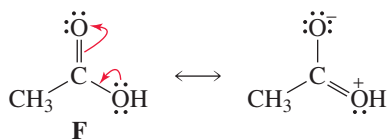
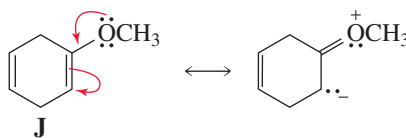
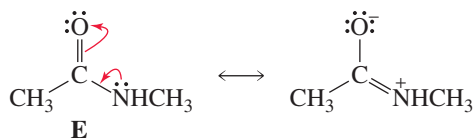
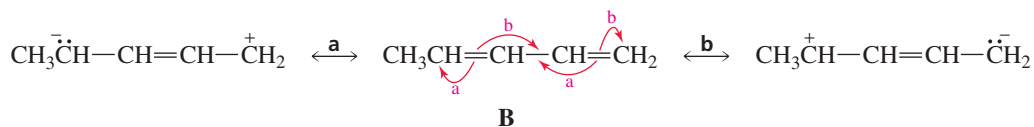
PROBLEM 6 Answer

$\ddot{O}H$ ⟷ $\overset{+}{O}H$ ⟷ $\overset{+}{O}H$ ⟷ $\overset{+}{O}H$ ⟷ $\ddot{O}H$

PROBLEM 7 Answer

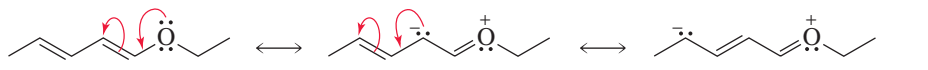
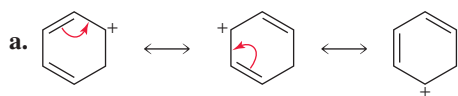
B, E, F, H, J, M, and O

PROBLEM 8 Answer

$CH_3\overset{-}{\ddot{C}}H-CH=CH-\overset{+}{C}H_2$ ⟷(a) $CH_3CH=CH-CH=CH_2$ (B) ⟷(b) $CH_3\overset{+}{C}H-CH=CH-\overset{-}{\ddot{C}}H_2$

E, J, F, M, H, O

PROBLEM 9 Answer

PROBLEM 10 Answer

a.

b. Notice in the following example that the electrons can move either clockwise or counterclockwise:

c.

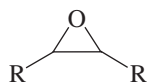
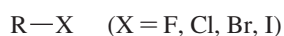
d. $CH_2=CH-CH=CH-\ddot{N}H_2$ ⟷ $CH_2=CH-\overset{-}{\ddot{C}}H-CH=\overset{+}{N}H_2$ ⟷ $\overset{-}{\ddot{C}}H_2-CH=CH-CH=\overset{+}{N}H_2$

e. Notice in the following example that the lone-pair electrons can be moved toward either of the two sp^2 carbons:

f.

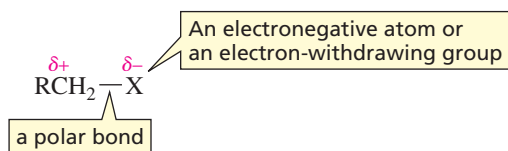
8 Substitution and Elimination Reactions of Alkyl Halides

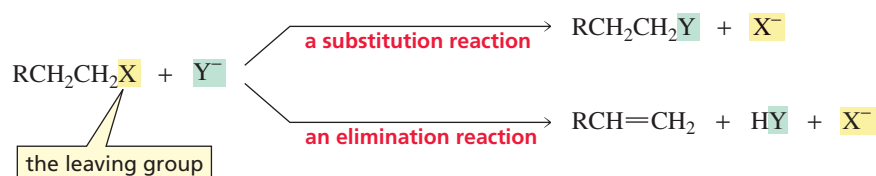
This cartoon was published in *Time Magazine* on June 30, 1947.

In this chapter you will see how the widespread use of DDT gave birth to the environmental movement. You will also learn why life is based on carbon rather than on silicon, even though silicon is just below carbon in the periodic table and is far more abundant than carbon in Earth's crust.

We have seen that the families of organic compounds can be placed in one of four groups, and that all the families in a group react in similar ways (Section 5.2). This chapter begins our discussion of the families of compounds in Group III.

Group III

R—X (X = F, Cl, Br, I)
R—OH
R—OR
R–epoxide–R (O)

Notice that all the families in Group III have an electronegative atom or an electron-withdrawing group attached to an sp^3 carbon. This atom or group creates a polar bond that allows the compound to undergo substitution and/or elimination reactions.

*In a **substitution reaction,** the electronegative atom or electron-withdrawing group is replaced by another atom or group.*

*In an **elimination reaction,** the electronegative atom or electron-withdrawing group is eliminated, along with a hydrogen from an adjacent carbon.*

The atom or group that is *substituted* or *eliminated* is called a **leaving group.**

This chapter focuses on the *substitution and elimination reactions* of alkyl halides—compounds in which the leaving group is a halide ion (F^-, Cl^-, Br^-, or I^-).*

alkyl halides

R—F	R—Cl	R—Br	R—I
an alkyl fluoride	**an alkyl chloride**	**an alkyl bromide**	**an alkyl iodide**

Alkyl halides are a good family of compounds with which to start the study of substitution and elimination reactions because they have relatively good leaving groups; that is, the halide ions are easily displaced. After learning about the reactions of alkyl halides, you will be prepared to move on to Chapter 9, which discusses the substitution and elimination reactions of compounds with poorer leaving groups (those that are more difficult to displace).

Substitution and elimination reactions are important in organic chemistry because they make it possible to convert readily available alkyl halides into a wide variety of other compounds. Substitution and elimination reactions are also important in the cells of plants and animals. Because cells exist in predominantly aqueous environments and alkyl halides are insoluble in water, biological systems use compounds in which the group that is replaced is more polar than a halogen and, therefore, more water soluble. We will look at some of these compounds in Chapter 9.

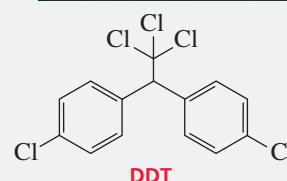
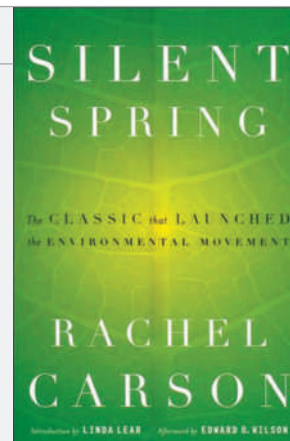
DDT: A Synthetic Organohalide That Kills Disease-Spreading Insects

Alkyl halides have been used as insecticides since 1939, when it was discovered that DDT (first synthesized in 1874) has a high toxicity to insects and a relatively low toxicity to mammals. DDT was used widely in World War II to control typhus and malaria in both the military and civilian populations. It saved millions of lives, but no one realized at that time that, because it is a very stable compound, it is resistant to biodegradation. In addition, DDT is not water soluble. Therefore, it accumulates in the fatty tissues of birds and fish and can be passed up the food chain. Most adults have a low concentration of DDT in their bodies.

In 1962, Rachel Carson, a marine biologist, published *Silent Spring,* where she pointed out the environmental impacts of the widespread use of DDT. The book was widely read, so it brought the problem of environmental pollution to the attention of the general public for the first time. Consequently, its publication was an important event in the birth of the environmental movement. Because of the concern it raised, DDT was banned in the United States in 1972. In 2004, the Stockholm Convention banned the worldwide use of DDT except for the control of malaria in countries where the disease is a major health problem.

In Section 14.8, we will look at the environmental effects caused by other synthetic organohalides known as chlorofluorohydrocarbons (CFCs).

Cl Cl Cl Cl Cl

DDT

PROBLEM 1

Methoxychlor is an insecticide that was intended to take DDT's place because it is not as soluble in fatty tissues and is more readily biodegradable. It, too, can accumulate in the environment, however, so its use was also banned—in 2002 in the European Union and in 2003 in the United States. Why is methoxychlor less soluble in fatty tissues than DDT?

Cl Cl Cl O O

methoxychlor

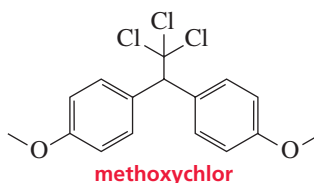



*Table 1.3 shows that carbon and iodine have the same electronegativity. However, iodine's large electron cloud causes it to be easily distorted. As a result, the C—I bond reacts as if it were polar.

8.1 THE MECHANISM FOR AN S_N2 REACTION

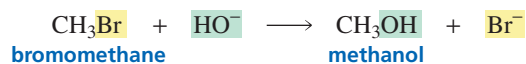
You will see that there are two different mechanisms by which a substitution reaction can take place. As you would expect, each of these mechanisms involves the *reaction of a nucleophile with an electrophile*. In both mechanisms, the nucleophile replaces the leaving group, so the substitution reaction is more precisely called a **nucleophilic substitution reaction.**

Now that you have seen the mechanisms for many different reactions, you might be wondering how these mechanisms are determined. Remember that a mechanism describes the step-by-step process by which reactants are converted into products. It is a theory that fits the accumulated experimental evidence pertaining to the reaction. Thus, *mechanisms are determined experimentally*. They are not something that chemists make up in an attempt to explain how a reaction occurs.

Experimental Evidence for the Mechanism for an S_N2 Reaction

We can learn a great deal about a reaction's mechanism by studying its **kinetics**—the factors that affect the rate of the reaction.

For example, the rate of the following nucleophilic substitution reaction depends on the concentrations of both reactants. If the concentration of the alkyl halide (bromomethane) is doubled, the rate of the reaction doubles. Likewise, if the concentration of the nucleophile (hydroxide ion) is doubled, the rate of the reaction doubles. If the concentrations of both reactants are doubled, the rate of the reaction quadruples.

$$\underset{\text{bromomethane}}{CH_3Br} + HO^- \longrightarrow \underset{\text{methanol}}{CH_3OH} + Br^-$$

Because we know the relationship between the rate of the reaction and the concentration of the reactants, we can write a **rate law** for the reaction:

$$\textbf{rate} \propto [\textbf{alkyl halide}][\textbf{nucleophile}]$$

The proportionality sign ($\propto$) can be replaced by an equal sign and a proportionality constant (k).

$$\textbf{rate} = \underset{\text{the rate constant}}{k}\,[\textbf{alkyl halide}][\textbf{nucleophile}]$$

The proportionality constant is called a **rate constant.** The magnitude of the rate constant for a reaction indicates how difficult it is for the reactants to overcome the energy barrier of the reaction—that is, how hard it is to reach the transition state (Section 5.3). The larger the rate constant, the lower is the energy barrier and, therefore, the easier it is for the reactants to reach the transition state (see Figure 8.2).

The **rate law** tells us which molecules are involved in the transition state of the rate-determining step of the reaction. Thus, the rate law for the reaction of bromomethane with hydroxide ion tells us that *both* bromomethane and hydroxide ion are involved in the rate-determining transition state.

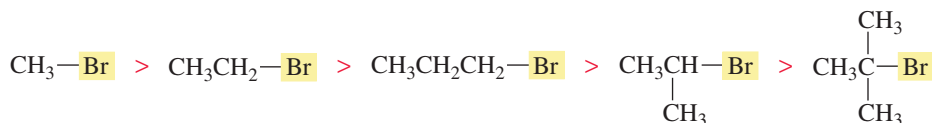
PROBLEM 2♦

How would the rate of the reaction between bromomethane and hydroxide ion be affected if the following changes in concentration are made?

a. The concentration of the alkyl halide is not changed and the concentration of the nucleophile is tripled.
b. The concentration of the alkyl halide is cut in half and the concentration of the nucleophile is not changed.

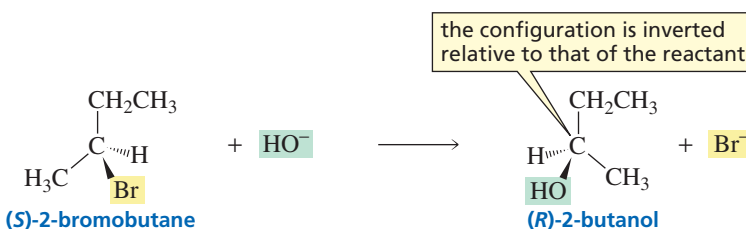
The reaction of bromomethane with hydroxide ion is an example of an **S_N2 reaction,** where "S" stands for substitution, "N" for nucleophilic, and "2" for bimolecular. **Bimolecular** means that two molecules are involved in the transition state of the rate-determining step. In 1937, Edward Hughes and Christopher Ingold proposed a mechanism for an S_N2 reaction. They based their mechanism on the following three pieces of *experimental evidence*:

1. The rate of the substitution reaction depends on the concentration of the alkyl halide *and* on the concentration of the nucleophile, indicating that both reactants are involved in the transition state of the rate-determining step.
2. As the alkyl group becomes larger, the rate of the substitution reaction with a given nucleophile becomes slower.

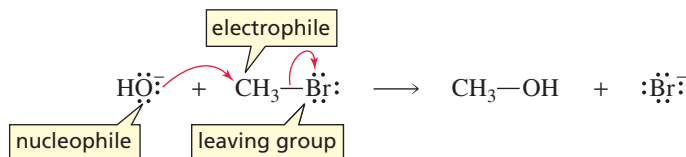
relative rates of an S_N2 reaction

$CH_3—Br > CH_3CH_2—Br > CH_3CH_2CH_2—Br > CH_3CH(CH_3)—Br > CH_3C(CH_3)_2—Br$

3. The substitution reaction of an alkyl halide in which the halogen is bonded to an asymmetric center leads to the formation of only one stereoisomer, and the configuration of the asymmetric center in the product is inverted relative to its configuration in the reacting alkyl halide.

the configuration is inverted relative to that of the reactant

(*S*)-2-bromobutane + HO^- ⟶ (*R*)-2-butanol + Br^-

The Mechanism for an S_N2 Reaction

Using the preceding evidence, Hughes and Ingold proposed the following one-step mechanism for an S_N2 reaction:

MECHANISM FOR THE S_N2 REACTION OF AN ALKYL HALIDE

An S_N2 reaction is a one-step reaction.

HO^- (nucleophile) + $CH_3—Br$ (electrophile; leaving group) ⟶ $CH_3—OH$ + Br^-

A nucleophile attacks the back side of the carbon that is bonded to the leaving group.

- The nucleophile attacks the back side of the carbon (the electrophile) that bears the leaving group and displaces it.

A productive collision is one that leads to the formation of the product. A productive collision in an S_N2 reaction requires the nucleophile to hit the carbon on the side opposite the side that is bonded to the leaving group. Therefore, the carbon is said to undergo **back-side attack.**

How the Mechanism Accounts for the Experimental Evidence

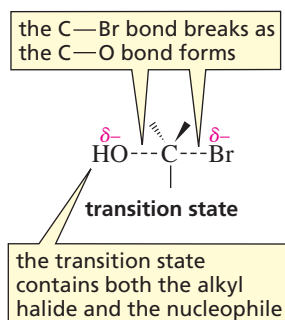
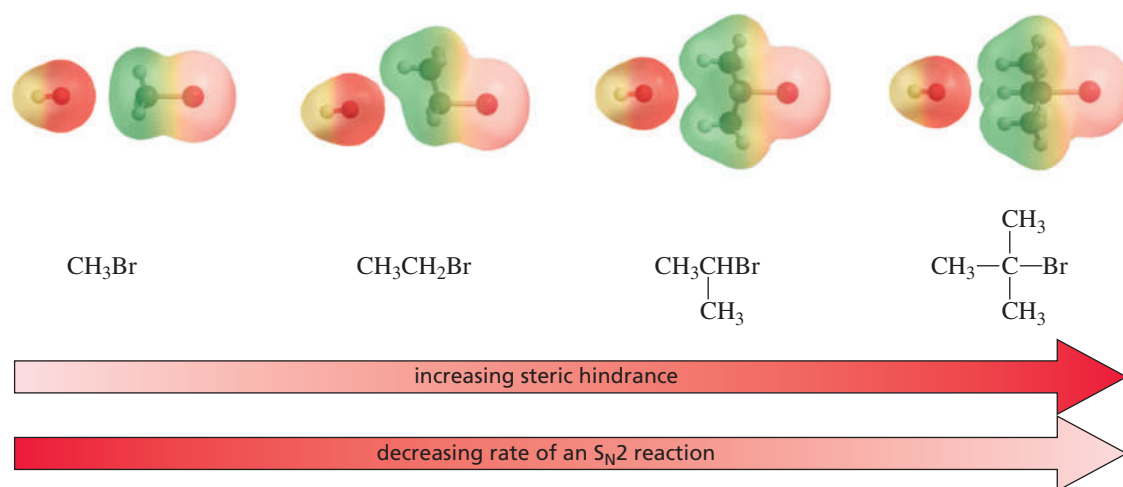
How does Hughes and Ingold's mechanism account for the three pieces of experimental evidence? The mechanism shows that the alkyl halide and the nucleophile are both in the

transition state of the one-step reaction. Therefore, increasing the concentration of either of them makes their collision more probable, so the rate of the reaction will depend on the concentration of both, exactly as observed.

the C—Br bond breaks as the C—O bond forms

$\overset{\delta-}{HO}$---C---$\overset{\delta-}{Br}$

transition state

the transition state contains both the alkyl halide and the nucleophile

Bulky substituents attached to the carbon that undergoes back-side attack will decrease the nucleophile's access to the back side of the carbon and will therefore decrease the rate of the reaction (Figure 8.1). This explains why, as the size of the alkyl group increases, the rate of the substitution reaction decreases.

▲ Figure 8.1
The approach of HO^- (shown by the red and yellow ball) to the back side of the carbon of methyl bromide, a carbon of a primary alkyl bromide, a carbon of a secondary alkyl bromide, and a carbon of a tertiary alkyl bromide. Increasing the bulk of the substituents bonded to the carbon that is undergoing nucleophilic attack decreases access to the back side of the carbon, thereby decreasing the rate of the S_N2 reaction.

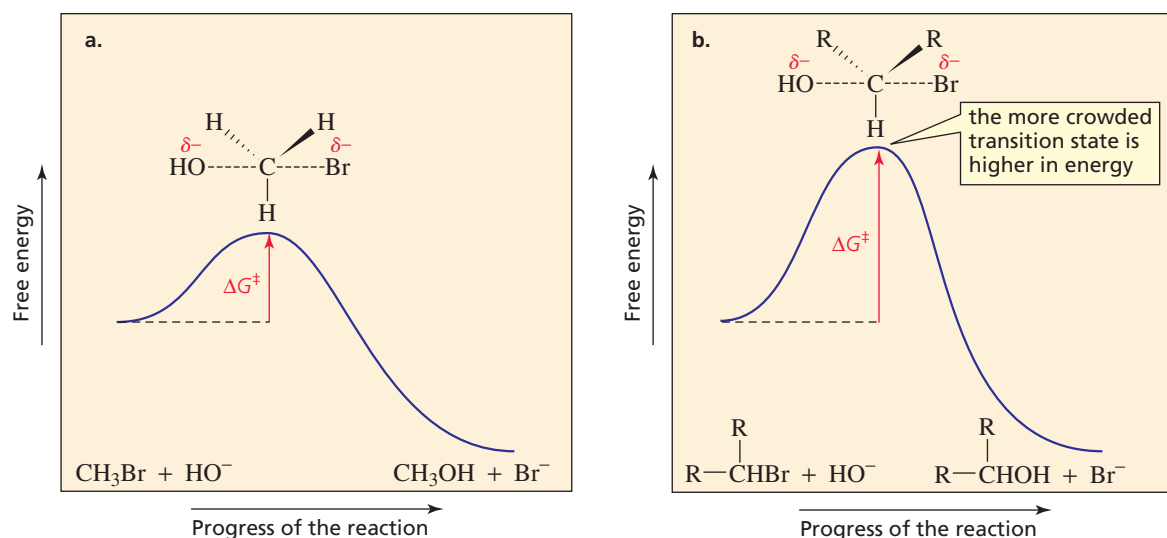
Steric effects are effects caused by the fact that groups occupy a certain volume of space. A steric effect that decreases reactivity is called **steric hindrance.** This occurs when groups are in the way at a reaction site. It is steric hindrance that causes alkyl halides to have the following relative reactivities in an S_N2 reaction because primary alkyl halides are usually less sterically hindered than secondary alkyl halides, and secondary alkyl halides are less sterically hindered than tertiary alkyl halides (Figure 8.2).

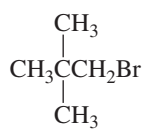
The relative lack of steric hindrance causes methyl halides and primary alkyl halides to be the most reactive alkyl halides in S_N2 reactions.

Tertiary alkyl halides cannot undergo S_N2 reactions.

relative reactivities of alkyl halides in an S_N2 reaction

most reactive → methyl halide > 1° alkyl halide > 2° alkyl halide > 3° alkyl halide ← too unreactive to undergo an S_N2 reaction

The three alkyl groups of a tertiary alkyl halide make it impossible for the nucleophile to come within bonding distance of the tertiary carbon, so tertiary alkyl halides cannot undergo S_N2 reactions.

▲ **Figure 8.2**
The reaction coordinate diagrams show that steric hindrance decreases the rate of the reaction by increasing the energy of the transition state:
(a) the S_N2 reaction of *unhindered* bromomethane with hydroxide ion
(b) an S_N2 reaction of a *sterically hindered* secondary alkyl bromide with hydroxide ion

$$\begin{array}{c} CH_3 \\ | \\ CH_3CCH_2Br \\ | \\ CH_3 \end{array}$$

1-bromo-2,2-dimethylpropane

Although this is a primary alkyl halide, it undergoes S_N2 reactions very slowly because its single alkyl group is unusually bulky.

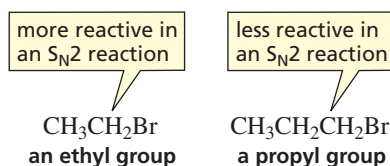
The rate of an S_N2 reaction depends not only on the *number* of alkyl groups attached to the carbon that is undergoing nucleophilic attack, but also on their size. For example, bromoethane and 1-bromopropane are both primary alkyl halides, but bromoethane is more than twice as reactive in an S_N2 reaction, because the bulkier alkyl group on the carbon undergoing nucleophilic attack in 1-bromopropane provides more steric hindrance to back-side attack.

An S_N2 reaction takes place with inversion of configuration.

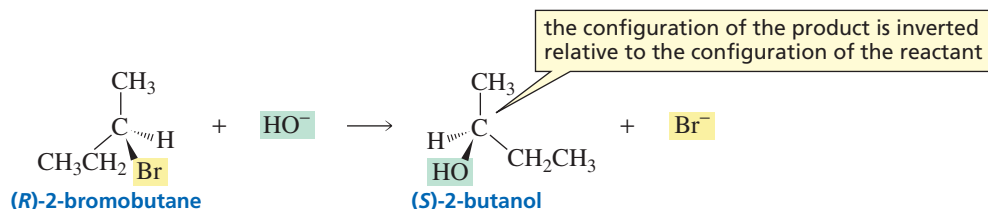
Figure 8.3 illustrates the third piece of experimental evidence used by Hughes and Ingold to arrive at their proposed mechanism—namely, the **inversion of configuration** at the carbon undergoing substitution.

As the nucleophile approaches the back side of the tetrahedral carbon, the C—H bonds begin to move away from the nucleophile and its attacking electrons.

The C—H bonds in the transition state are all in the same plane, and the carbon is pentacoordinate (fully bonded to three atoms and partially bonded to two) rather than tetrahedral.

The C—H bonds have continued to move in the same direction. When the bond between carbon and the nucleophile is fully formed, and the bond between carbon and bromine is completely broken, carbon is once again tetrahedral.

▲ **Figure 8.3**
The reaction between hydroxide ion and bromomethane, showing that the carbon at which substitution occurs in an S_N2 reaction inverts its configuration, just like an umbrella can invert in a windstorm.

Because an S_N2 reaction takes place with inversion of configuration, only one substitution product is formed when an alkyl halide whose halogen atom is bonded to an asymmetric center undergoes an S_N2 reaction. The configuration of that product is inverted relative to the configuration of the alkyl halide. For example, the substitution product obtained from the reaction of hydroxide ion with (*R*)-2-bromobutane is (*S*)-2-butanol.

If the leaving group is attached to an asymmetric center, an S_N2 reaction forms only the stereoisomer with the inverted configuration.

To draw the inverted product of an S_N2 reaction, draw the mirror image of the reactant and replace the halogen with the nucleophile.

the configuration of the product is inverted relative to the configuration of the reactant

CH_3, C, H, CH_3CH_2, Br + HO^- ⟶ CH_3, C, H, HO, CH_2CH_3 + Br^-

(*R*)-2-bromobutane **(*S*)-2-butanol**

PROBLEM 3♦

Does increasing the energy barrier for an S_N2 reaction increase or decrease the magnitude of the rate constant for the reaction?

PROBLEM 4♦

Arrange the following alkyl bromides in order from most reactive to least reactive in an S_N2 reaction: 1-bromo-2-methylbutane, 1-bromo-3-methylbutane, 2-bromo-2-methylbutane, and 1-bromopentane.

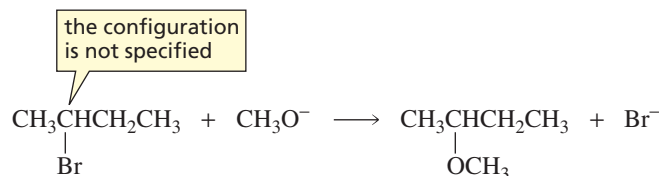
PROBLEM 5♦ Solved

Draw the products obtained from the S_N2 reaction of

a. 2-bromobutane and methoxide ion.
b. (*R*)-2-bromobutane and methoxide ion.
c. (*S*)-3-chlorohexane and hydroxide ion.
d. 3-iodopentane and hydroxide ion.

Solution to 5a The product is 2-methoxybutane. Because the reaction is an S_N2 reaction, we know that the configuration of the product is inverted relative to the configuration of the reactant. The configuration of the reactant is not specified, however, so we cannot specify the configuration of the product. In other words, because we do not know if the reactant is *R* or *S* or a mixture of the two, we also do not know if the product is *R* or *S* or a mixture of the two.

the configuration is not specified

$CH_3CH(Br)CH_2CH_3 + CH_3O^- \longrightarrow CH_3CH(OCH_3)CH_2CH_3 + Br^-$

PROBLEM 6 Solved

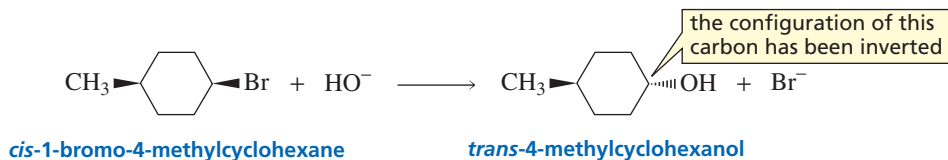
Draw the substitution products that will be formed from the following S_N2 reactions:

a. *cis*-1-bromo-4-methylcyclohexane and hydroxide ion
b. *trans*-1-iodo-4-ethylcyclohexane and methoxide ion
c. *cis*-1-chloro-3-methylcyclobutane and ethoxide ion

Solution to 6a Only the trans product is obtained in this S_N2 reaction because the carbon bonded to the leaving group is attacked by the nucleophile on its back side.

the configuration of this carbon has been inverted

CH_3–cyclohexane–Br + HO^- ⟶ CH_3–cyclohexane–OH + Br^-

***cis*-1-bromo-4-methylcyclohexane** ***trans*-4-methylcyclohexanol**

8.2 FACTORS THAT AFFECT S_N2 REACTIONS

We will now look at how the nature of the leaving group and the nature of the nucleophile affect an S_N2 reaction.

The Leaving Group in an S_N2 Reaction

If an alkyl iodide, an alkyl bromide, an alkyl chloride, and an alkyl fluoride with the same alkyl group were allowed to react with the same nucleophile under the same conditions, we would find that the alkyl iodide is the most reactive and the alkyl fluoride is the least reactive.

Reaction	relative rates of reaction	pK_a values of HX
$HO^- + RCH_2I \longrightarrow RCH_2OH + I^-$	30,000	–10
$HO^- + RCH_2Br \longrightarrow RCH_2OH + Br^-$	10,000	–9
$HO^- + RCH_2Cl \longrightarrow RCH_2OH + Cl^-$	200	–7
$HO^- + RCH_2F \longrightarrow RCH_2OH + F^-$	1	3.2

The only difference between these four reactions is the nature of the leaving group. From the relative reaction rates, we see that iodide ion is the best leaving group and fluoride ion is the worst. This brings us to an important rule in organic chemistry that you will encounter frequently: when comparing bases of the same type, *the weaker the basicity of a group, the better is its leaving propensity*.

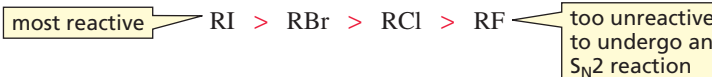
The reason leaving propensity depends on basicity is that *weak bases are stable bases;* they readily bear the electrons they formerly shared with a proton. Therefore, they do not share their electrons well. Thus, a weak base is not bonded as strongly to the carbon as a strong base would be, and a weaker bond is more readily broken.

We have seen that iodide ion is the weakest base of the halide ions (it has the strongest conjugate acid; Section 2.6) and fluoride ion is the strongest base (it has the weakest conjugate acid). Therefore, when comparing alkyl halides with the same alkyl group, we find that the alkyl iodide is the most reactive and the alkyl fluoride is the least reactive. In fact, the fluoride ion is such a strong base that alkyl fluorides essentially do not undergo S_N2 reactions.

The weaker the base, the better it is as a leaving group.

Stable bases are weak bases.

relative reactivities of alkyl halides in an S_N2 reaction

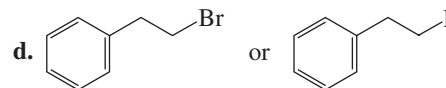
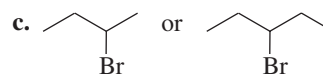
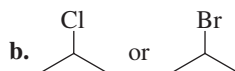
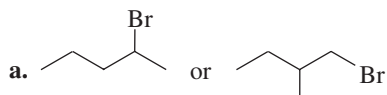
most reactive → RI > RBr > RCl > RF ← too unreactive to undergo an S_N2 reaction

PROBLEM 7♦

Which alkyl halide would you expect to be more reactive in an S_N2 reaction with a given nucleophile? In each case, you can assume that both alkyl halides have the same stability.

a. Br or Br

b. Cl or Br

c. Br or Br

d. Br or I

The Nucleophile in an S_N2 Reaction

When we talk about atoms or molecules that have lone-pair electrons, sometimes we call them bases and sometimes we call them nucleophiles. What is the difference between a base and a nucleophile?

Basicity is a measure of how well a compound (a **base**) shares its lone pair with a proton. The stronger the base, the better it shares its electrons.

Nucleophilicity is a measure of how readily a compound (a **nucleophile**) is able to attack an electron-deficient atom. In the case of an S_N2 reaction, nucleophilicity is a measure of how readily the nucleophile attacks an sp^3 carbon bonded to a leaving group.

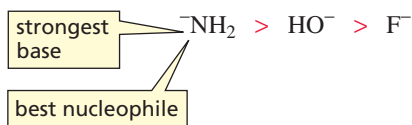
Because the nucleophile attacks an sp^3 carbon in the rate-determining step of an S_N2 reaction, the rate of the reaction will depend on the strength of the nucleophile: *the better the nucleophile, the faster the rate of the S_N2 reaction.*

The better the nucleophile, the faster the rate of an S_N2 reaction.

If the attacking atoms are about the same size, *stronger bases are better nucleophiles*. For example, comparing attacking atoms in the first row of the periodic table, the amide ion is both the strongest base and the best nucleophile (Section 2.6). Notice that bases are described as being strong or weak, whereas nucleophiles are described as being good or poor.

relative base strengths and relative nucleophilicities

$$^-NH_2 > HO^- > F^-$$

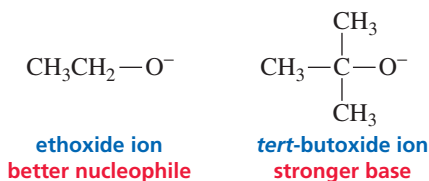
strongest base (points to $^-NH_2$)
best nucleophile (points to $^-NH_2$)

A species with a negative charge is a stronger base *and* a better nucleophile than a species that has the same attacking atom but is neutral. Thus, HO^- is a stronger base and a better nucleophile than H_2O.

stronger base, better nucleophile		weaker base, poorer nucleophile
HO^-	>	H_2O
CH_3O^-	>	CH_3OH
$^-NH_2$	>	NH_3
$CH_3CH_2NH^-$	>	$CH_3CH_2NH_2$

Nucleophilicity Is Affected by Steric Effects

Nucleophilicity is *affected* by steric effects. A bulky nucleophile cannot approach the back side of a carbon as easily as a less sterically hindered nucleophile can. Basicity, on the other hand, is relatively *unaffected* by steric effects because a base removes an unhindered proton.

$CH_3CH_2-O^-$ — ethoxide ion, better nucleophile

$CH_3-C(CH_3)_2-O^-$ — *tert*-butoxide ion, stronger base

Therefore, *tert*-butoxide ion, with its three methyl groups, is a poorer nucleophile than ethoxide ion, even though *tert*-butoxide ion is a stronger base (pK_a of *tert*-butanol = 18) than ethoxide ion (pK_a of ethanol = 16).

PROBLEM 8♦

Which reaction in each of the following pairs occurs faster?

a. $CH_3CH_2Br + H_2O$ or $CH_3CH_2Br + HO^-$

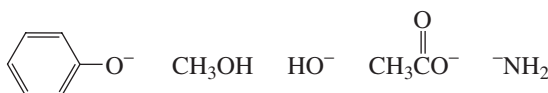
b. $CH_3CH_2Cl + CH_3O^-$ or $CH_3CH_2Cl + CH_3OH$

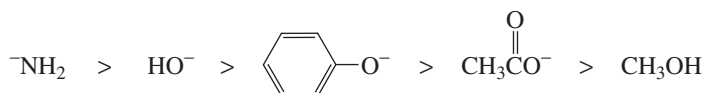
PROBLEM 9

a. Which is a better nucleophile, CH_3OH or CH_3NH_2?
b. Which is a stronger base?

PROBLEM 10 Solved

List the following species in order from best nucleophile to poorest nucleophile:

$$C_6H_5O^- \quad CH_3OH \quad HO^- \quad CH_3\overset{O}{\overset{\|}{C}}O^- \quad {}^-NH_2$$

Solution Let's first divide the nucleophiles into groups. There is one nucleophile with a negatively charged nitrogen, three with negatively charged oxygens, and one with a neutral oxygen. We know that the nucleophile with the negatively charged nitrogen is the best nucleophile because it is the strongest base. We also know that the poorest nucleophile is the one with the neutral oxygen. To complete the problem, we need to rank the three nucleophiles with negatively charged oxygens, which we can do by looking at the pK_a values of their conjugate acids. A carboxylic acid is a stronger acid than phenol, which is a stronger acid than water (Section 7.8). Because water is the weakest acid, its conjugate base is the strongest base and the best nucleophile. Thus, the relative nucleophilicities are:

$${}^-NH_2 > HO^- > C_6H_5O^- > CH_3\overset{O}{\overset{\|}{C}}O^- > CH_3OH$$

Many different kinds of nucleophiles can react with alkyl halides. Therefore, a wide variety of organic compounds can be synthesized by means of S_N2 reactions.

$$CH_3CH_2Cl + HO^- \longrightarrow CH_3CH_2OH + Cl^-$$
an alcohol

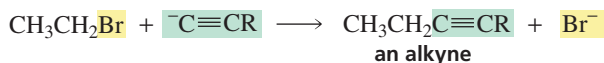
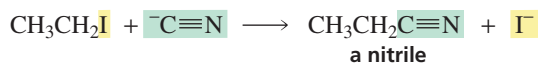
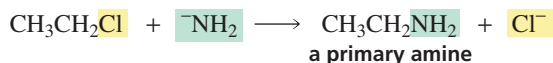
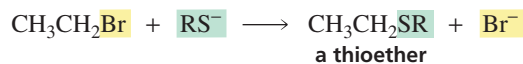
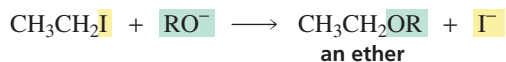
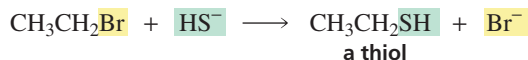
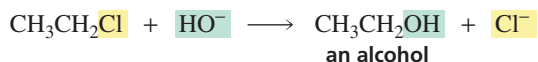
$$CH_3CH_2Br + HS^- \longrightarrow CH_3CH_2SH + Br^-$$
a thiol

$$CH_3CH_2I + RO^- \longrightarrow CH_3CH_2OR + I^-$$
an ether

$$CH_3CH_2Br + RS^- \longrightarrow CH_3CH_2SR + Br^-$$
a thioether

$$CH_3CH_2Cl + {}^-NH_2 \longrightarrow CH_3CH_2NH_2 + Cl^-$$
a primary amine

$$CH_3CH_2I + {}^-C\equiv N \longrightarrow CH_3CH_2C\equiv N + I^-$$
a nitrile

$$CH_3CH_2Br + {}^-C\equiv CR \longrightarrow CH_3CH_2C\equiv CR + Br^-$$
an alkyne

PROBLEM 11♦

What is the product of the reaction of bromoethane with each of the following nucleophiles?

a. $CH_3CH_2CH_2O^-$ **b.** $CH_3C\equiv C^-$ **c.** $(CH_3)_3N$ **d.** $CH_3CH_2S^-$

Why Are Living Organisms Composed of Carbon Instead of Silicon?

There are two reasons living organisms are composed primarily of carbon, oxygen, nitrogen, and hydrogen: the *fitness* of these elements for specific roles in life processes and their *availability* in the environment. Fitness apparently was more important than availability because carbon rather than silicon became the fundamental building block of living organisms despite the fact that silicon, which is just below carbon in the periodic table, is more than 140 times more abundant than carbon in Earth's crust.

Why are carbon, oxygen, nitrogen, and hydrogen so well suited for the roles they play in living organisms? First and foremost, they are among the smallest atoms that form covalent bonds and they can form multiple bonds. Because of these factors, they form strong bonds (which means the molecules containing them are stable). The compounds that make up living organisms must be stable and therefore slow to react if the organisms are to survive.

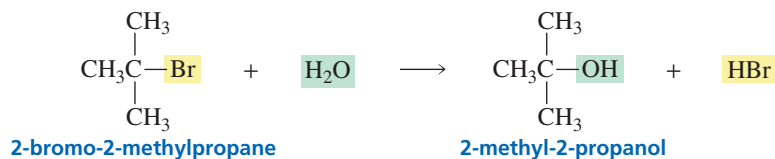
Silicon has almost twice the diameter of carbon, so silicon forms longer and weaker bonds. Consequently, an S_N2 reaction at silicon would occur much more rapidly than an S_N2 reaction at carbon. Moreover, silicon has another problem. The end product of carbon metabolism is CO_2. The analogous product of silicon metabolism would be SiO_2. But unlike carbon, which is doubly bonded to oxygen in CO_2, silicon is only singly bonded to oxygen in SiO_2. Therefore, silicon dioxide molecules polymerize to form quartz (sand). It is hard to imagine that life could exist, much less proliferate, if animals exhaled sand instead of CO_2!

	Abundance (atoms/100 atoms)	
Element	**In living organisms**	**In Earth's crust**
H	49	0.22
C	25	0.19
O	25	47
N	0.3	0.1
Si	0.03	28

8.3 THE MECHANISM FOR AN S_N1 REACTION

Given our understanding of an S_N2 reaction, we would expect the rate of the following reaction to be very slow because water is a poor nucleophile and the alkyl halide is sterically hindered to back-side attack.

$$(CH_3)_3C{-}Br + H_2O \longrightarrow (CH_3)_3C{-}OH + HBr$$

2-bromo-2-methylpropane → 2-methyl-2-propanol

It turns out, however, that the reaction is surprisingly fast. In fact, it is over 1 million times faster than the reaction of bromomethane (a compound with no steric hindrance) with water. The reaction, therefore, must be taking place by a mechanism different from that of an S_N2 reaction.

Experimental Evidence for the Mechanism of an S_N1 Reaction

We have seen that in order to determine the mechanism of a reaction, we need to find out what factors affect the rate of the reaction, and we need to know the configuration of the products of the reaction.

Doubling the concentration of the alkyl halide doubles the rate of the reaction, but changing the concentration of the nucleophile has no effect on its rate. This knowledge allows us to write a rate law for the reaction:

$$\textbf{rate} = k[\textbf{alkyl halide}]$$

Because the rate law for the reaction of 2-bromo-2-methylpropane with water differs from the rate law for the reaction of bromomethane with hydroxide ion (Section 8.1), the two reactions must have different mechanisms.

We have seen that the reaction between bromomethane and hydroxide ion is an S_N2 reaction. The reaction between 2-bromo-2-methylpropane and water is an **S_N1 reaction,** where "S" stands for *substitution,* "N" stands for *nucleophilic,* and "1" stands for *unimolecular*. **Unimolecular** means that only one molecule is involved in the transition state of the rate-determining step.

The mechanism for an S_N1 reaction is based on the following experimental evidence:

1. The rate law shows that the rate of the reaction depends only on the concentration of the alkyl halide, so only the alkyl halide is involved in the transition state of the rate-determining step.
2. Only tertiary alkyl halides undergo S_N1 reactions with poor nucleophiles such as water and alcohols.*
3. The substitution reaction of an alkyl halide in which the halogen is bonded to an asymmetric center forms two stereoisomers: one with the same relative configuration as that of the reacting alkyl halide, and the other with the inverted configuration.

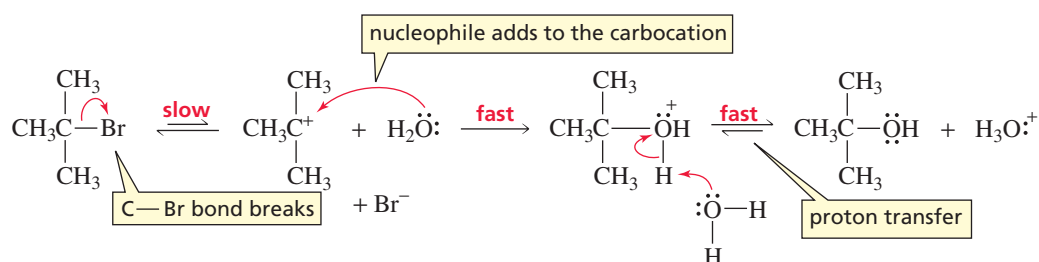
The Mechanism for an S_N1 Reaction

Unlike an S_N2 reaction, where the leaving group departs and the nucleophile approaches *at the same time*, the leaving group in an S_N1 reaction departs *before* the nucleophile approaches.

MECHANISM FOR THE S_N1 REACTION OF AN ALKYL HALIDE

$$(CH_3)_3C{-}Br \underset{\text{slow}}{\rightleftharpoons} (CH_3)_3C^+ + Br^- \qquad (CH_3)_3C^+ + H_2\ddot{O}: \xrightarrow{\text{fast}} (CH_3)_3C{-}\overset{+}{\ddot{O}}H_2$$

$$(CH_3)_3C{-}\overset{+}{\ddot{O}}H_2 + H_2\ddot{O}: \underset{\text{fast}}{\rightleftharpoons} (CH_3)_3C{-}\ddot{O}H + H_3O^+$$

nucleophile adds to the carbocation
C—Br bond breaks
proton transfer

- In the first step, the carbon–halogen bond breaks and the previously shared pair of electrons stays with the halogen. As a result, a carbocation intermediate is formed.
- In the second step, the nucleophile reacts rapidly with the carbocation (an electrophile) to form a protonated alcohol.
- Whether the alcohol product will exist in its protonated (acidic) form or neutral (basic) form depends on the pH of the solution. At pH = 7, the alcohol will exist predominantly in its neutral form (Section 2.10).

An S_N1 reaction is a two-step reaction.

Because the rate of an S_N1 reaction depends only on the concentration of the alkyl halide, the first step must be the slow (rate-determining) step (Figure 8.4). The nucleophile is not involved in the rate-determining step, so its concentration has no effect on the rate of the reaction.

*Murphy, T.J. *J. Chem. Ed.* **2009**, *86*, 519–524.

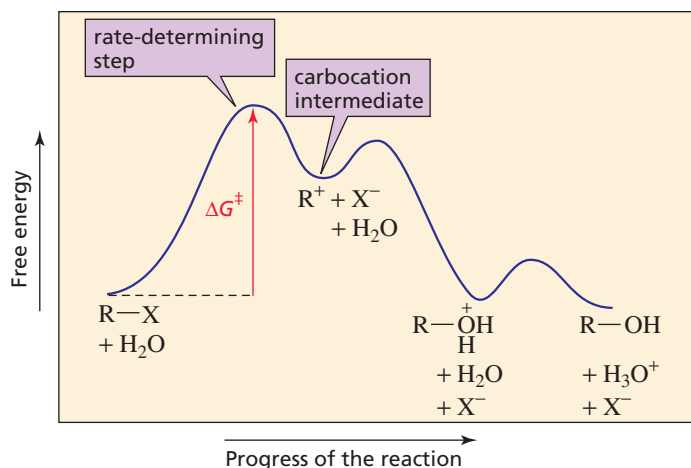



Figure 8.4
The reaction coordinate diagram for an S_N1 reaction shows why increasing the rate of the second step will not make an S_N1 reaction go any faster.

How the Mechanism Accounts for the Experimental Evidence

How does the mechanism for an S_N1 reaction account for the three pieces of experimental evidence?

First, because the alkyl halide is the only species that participates in the rate-determining step, the mechanism agrees with the observation that the rate of the reaction depends only on the concentration of the alkyl halide; it does not depend on the concentration of the nucleophile.

Second, the mechanism shows that a carbocation is formed in the rate-determining step. This explains why tertiary alkyl halides undergo S_N1 reactions, but primary and secondary alkyl halides do not. Tertiary carbocations are more stable than primary and secondary carbocations and, therefore, are the most easily formed.

Carbocation stability: 3° > 2° > 1°

Tertiary alkyl halides undergo S_N1 reactions. Primary and secondary alkyl halides undergo S_N2 reactions.

Third, the positively charged carbon of the carbocation intermediate is sp^2 hybridized, which means the three bonds connected to it are in the same plane (Figure 8.5). In the second step of the S_N1 reaction, the nucleophile can approach the carbocation from either side of the plane, so some of the product will have the same configuration as the reacting alkyl halide and some will have an inverted configuration.

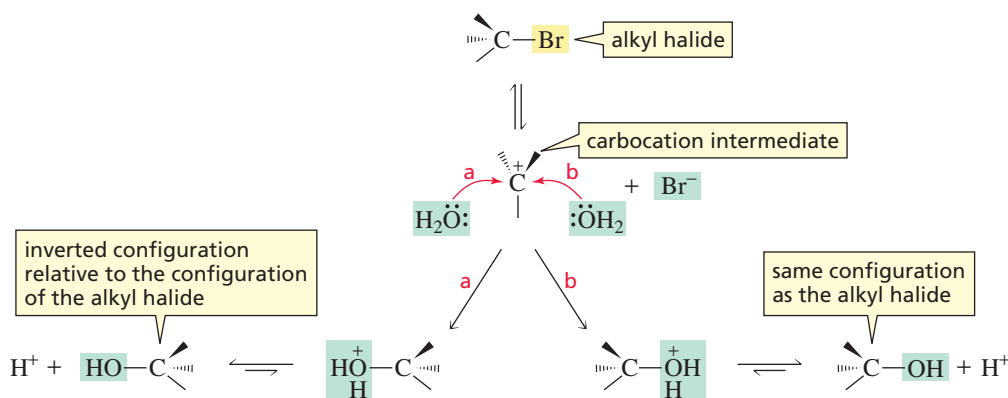



Figure 8.5
If the nucleophile adds to the *opposite side* of the carbon from which the leaving group departs (labeled a), then the product will have the *inverted* configuration relative to the configuration of the alkyl halide.
If the nucleophile adds to the side of the carbon from which the leaving group departs (labeled b), then the product will have the *same* relative configuration as that of the reacting alkyl halide.

Now we can understand why an S_N1 reaction of a tertiary alkyl halide in which the leaving group is attached to an asymmetric center forms two stereoisomers: addition of the nucleophile to one side of the planar carbocation intermediate forms one stereoisomer, and addition to the other side produces the other stereoisomer. Thus, the product is a pair of enantiomers (Section 6.6).

An S_N1 reaction takes place with inversion and retention of configuration.

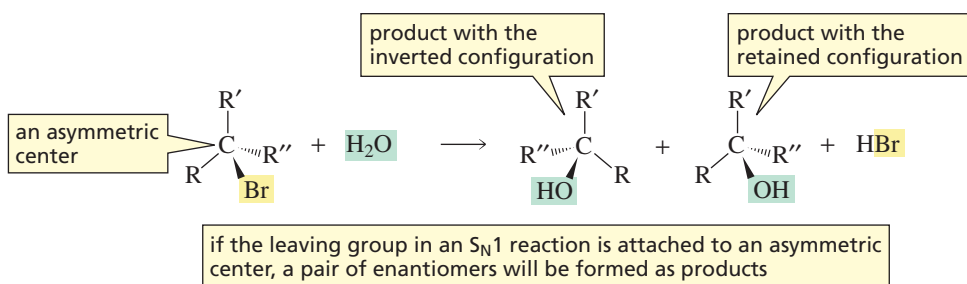
If the leaving group is attached to an asymmetric center, an S_N1 reaction forms a pair of enantiomers.

an asymmetric center

$$R'R''RC\text{–}Br + H_2O \longrightarrow R''R'RC\text{–}HO + R'RR''C\text{–}OH + HBr$$

product with the inverted configuration

product with the retained configuration

if the leaving group in an S_N1 reaction is attached to an asymmetric center, a pair of enantiomers will be formed as products

PROBLEM 12♦

Draw the substitution products that will be formed from the following S_N1 reactions:

a. 3-chloro-3-methylhexane and methanol **b.** 3-bromo-3-methylpentane and methanol

8.4 FACTORS THAT AFFECT S_N1 REACTIONS

We will now look at how the leaving group and the nucleophile affect S_N1 reactions.

The Leaving Group in an S_N1 Reaction

Because the rate-determining step of an S_N1 reaction is the formation of a carbocation, two factors affect the rate of the reaction:

1. the ease with which the leaving group dissociates
2. the stability of the carbocation that is formed

As in an S_N2 reaction, there is a direct relationship between basicity and leaving propensity in an S_N1 reaction: the weaker the base, the less tightly it is bonded to the carbon and the more easily the carbon–halogen bond can be broken. As a result, comparing alkyl halides with the same alkyl group, an alkyl iodide is the most reactive and an alkyl fluoride is the least reactive in both S_N1 and S_N2 reactions.

relative reactivities of alkyl halides in an S_N1 reaction

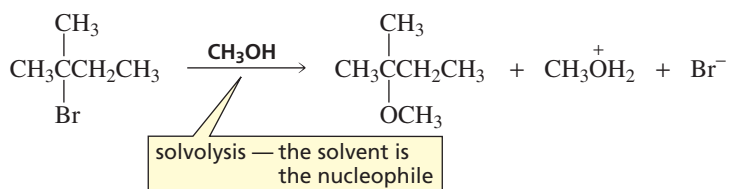
most reactive RI > RBr > RCl > RF least reactive

The Nucleophile in an S_N1 Reaction

Because the nucleophile does not participate in an S_N1 reaction until *after* the rate-determining step, the reactivity of the nucleophile has no effect on the rate of an S_N1 reaction.

In most S_N1 reactions, the solvent is the nucleophile. For example in the following reaction, methanol is both the nucleophile and the solvent. Reaction with a solvent is called **solvolysis.**

$$CH_3C(CH_3)(Br)CH_2CH_3 \xrightarrow{CH_3OH} CH_3C(CH_3)(OCH_3)CH_2CH_3 + CH_3\overset{+}{O}H_2 + Br^-$$

solvolysis — the solvent is the nucleophile

PROBLEM 13♦

Arrange the following alkyl halides in order from most reactive to least reactive in an S_N1 reaction: 2-bromo-2-methylpentane, 2-chloro-2-methylpentane, 3-chloropentane, and 2-iodo-2-methylpentane.

8.5 COMPARING S_N2 AND S_N1 REACTIONS

The characteristics of S_N2 and S_N1 reactions are compared in Table 8.1. Remember that the "2" in "S_N2" and the "1" in "S_N1" refer to the molecularity of the reaction (the number of molecules involved in the transition state of the rate-determining step) and *not* to the number of steps in the mechanism. In fact, the opposite is true: an S_N2 reaction proceeds by a *one*-step mechanism, whereas an S_N1 reaction proceeds by a *two*-step mechanism with a carbocation intermediate.

Table 8.1 Comparison of S_N2 and S_N1 Reactions

S_N2	S_N1
a one-step mechanism	a two-step mechanism with a carbocation intermediate
a bimolecular rate-determining step	a unimolecular rate-determining step
the rate is controlled by steric hindrance	the rate is controlled by the stability of the carbocation
methyl halides and primary and secondary alkyl halides undergo S_N2 reactions	only tertiary alkyl halides undergo S_N1 solvolysis reactions
product has the inverted configuration relative to that of the reactant	products have both the retained and inverted configurations relative to that of the reactant
the leaving group: $I^- > Br^- > Cl^- > F^-$	the leaving group: $I^- > Br^- > Cl^- > F^-$
the better the nucleophile, the faster the rate of the reaction	the strength of the nucleophile does not affect the rate of the reaction

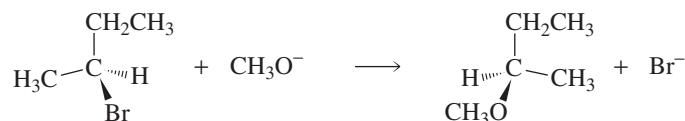
It is easy to tell whether an alkyl halide is going to undergo an S_N1 reaction or an S_N2 reaction. Just look at its structure. If the alkyl halide is a methyl halide or a primary or secondary alkyl halide, it will undergo an S_N2 reaction. If it is a tertiary alkyl halide, it will undergo an S_N1 reaction.

PROBLEM-SOLVING STRATEGY

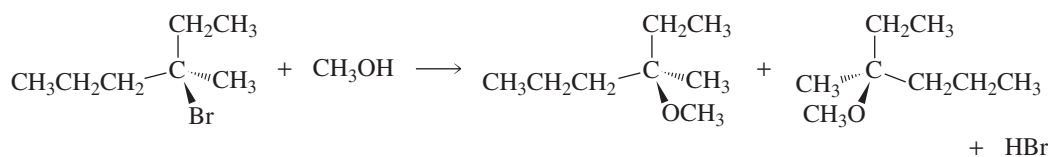
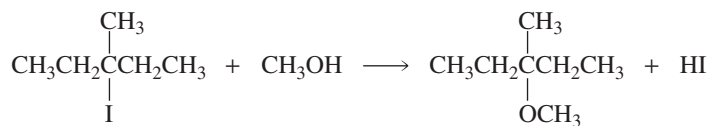
Predicting Whether a Nucleophilic Substitution Reaction Will Be an S_N1 Reaction or an S_N2 Reaction and Determining the Products of the Reaction

Draw the configuration(s) of the substitution product(s) that will be formed from the reactions of the following compounds with the indicated nucleophile:

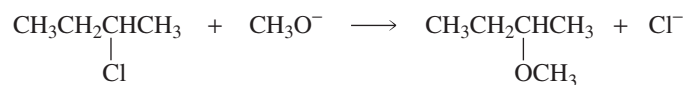
a. Because the reactant is a secondary alkyl halide, this is an S_N2 reaction. Therefore, the product will have the inverted configuration relative to the configuration of the reactant.

$$H_3C-C(CH_2CH_3)(H)(Br) + CH_3O^- \longrightarrow H-C(CH_2CH_3)(CH_3)(OCH_3) + Br^-$$

To draw the inverted product, draw the mirror image of the reacting alkyl halide and then put the nucleophile in the same location as the leaving group.

b. Because the reactant is a tertiary alkyl halide, this is an S_N1 reaction. Therefore, two substitution products will be obtained, one with the retained configuration and one with the inverted configuration, relative to the configuration of the reactant.

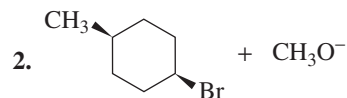
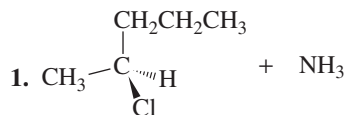
$$CH_3CH_2CH_2-C(CH_2CH_3)(CH_3)(Br) + CH_3OH \longrightarrow CH_3CH_2CH_2-C(CH_2CH_3)(CH_3)(OCH_3) + CH_3-C(CH_2CH_3)(CH_2CH_2CH_3)(CH_3O) + HBr$$

c. Because the reactant is a tertiary alkyl halide, this is an S_N1 reaction. The product does not have an asymmetric center, so it does not have stereoisomers. Therefore, only one product is formed.

$$CH_3CH_2C(CH_3)(I)CH_2CH_3 + CH_3OH \longrightarrow CH_3CH_2C(CH_3)(OCH_3)CH_2CH_3 + HI$$

d. Because the reactant is a secondary alkyl halide, this is an S_N2 reaction. Therefore, the configuration of the product will be inverted relative to the configuration of the reactant. But, since the configuration of the reactant is not indicated, we do not know the configuration of the product.

$$CH_3CH_2CH(Cl)CH_3 + CH_3O^- \longrightarrow CH_3CH_2CH(OCH_3)CH_3 + Cl^-$$

Now use the strategy you have just learned to solve Problem 14.

PROBLEM 14

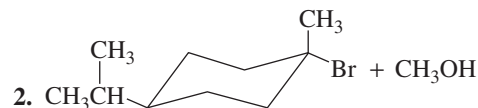
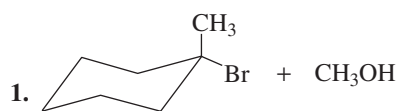
Draw the configuration(s) of the substitution product(s) that will be formed from the

a. S_N2 reaction of each of the following compounds with the indicated nucleophile:

1. CH_3—C(H)(Cl)($CH_2CH_2CH_3$) + NH_3

2. cyclohexane with CH_3 and Br + CH_3O^-

b. S_N1 reaction of each of the following compounds with the indicated nucleophile:

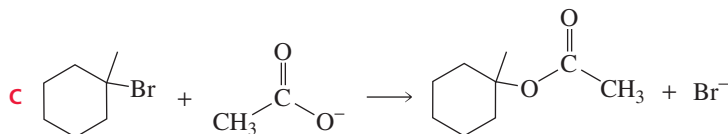
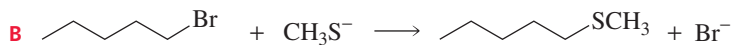
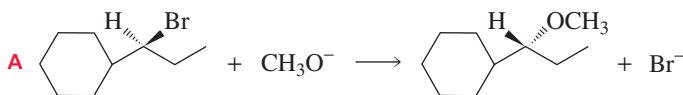
1. cyclohexane with CH_3 and Br + CH_3OH

2. $CH_3CH(CH_3)$–cyclohexane with CH_3 and Br + CH_3OH

PROBLEM 15♦

Which of the following reactions will go faster if the concentration of the nucleophile is increased?

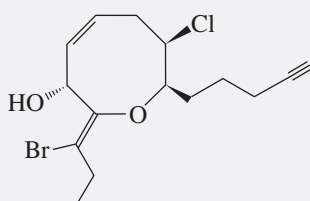
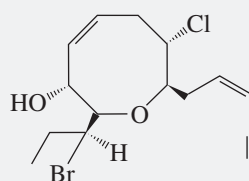
A: cyclohexyl–CH(Br)CH$_2$CH$_3$ (H, Br) + CH_3O^- $\longrightarrow$ cyclohexyl–CH(OCH$_3$)CH$_2$CH$_3$ (H, OCH$_3$) + Br^-

B: 1-bromopentane (Br) + CH_3S^- $\longrightarrow$ SCH_3 product + Br^-

C: 1-bromo-1-methylcyclohexane (Br) + $CH_3C(=O)O^-$ $\longrightarrow$ 1-methylcyclohexyl–O–C(=O)CH_3 + Br^-

Naturally Occurring Organohalides That Defend against Predators

a sea hare

For a long time, chemists thought that only a few organic compounds containing halogen atoms (organohalides) were found in nature. Now, however, over 5000 naturally occurring organohalides are known. Several marine organisms, including sponges, corals, and algae, synthesize organohalides that they use to deter predators. For example, red algae synthesize a toxic, foul-tasting organohalide that keeps predators from eating them. One predator that is not deterred, however, is a mollusk called a sea hare. After consuming red algae, a sea hare converts the algae's organohalide into a structurally similar compound that the sea hare uses for its own defense. Unlike other mollusks, a sea hare does not have a shell. Its method of defense is to surround itself with a slimy substance that contains the organohalide, thereby protecting itself from carnivorous fish.

Humans also synthesize organohalides to defend against infection. The human immune system has an enzyme that kills invading bacteria—another kind of predator—by halogenating them.

synthesized by red algae

synthesized by the sea hare

8.6 INTERMOLECULAR VERSUS INTRAMOLECULAR REACTIONS

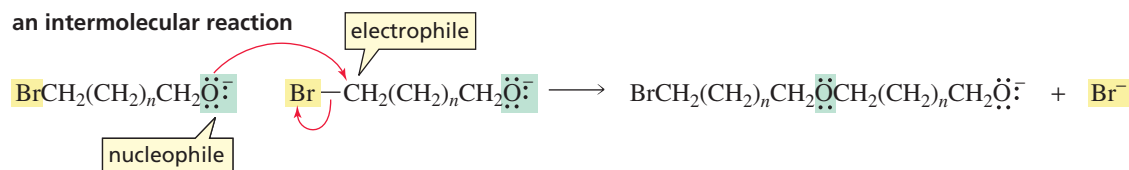
A molecule with two functional groups is called a **bifunctional molecule.** If the two functional groups are able to react with each other, then two kinds of reactions can occur—an *intermolecular* reaction and an *intramolecular* reaction. To understand the difference, let's look at a molecule with two functional groups that can react in an S_N2 reaction—namely, a good nucleophile (such as an alkoxide ion) and an alkyl halide.

If the alkoxide ion of one molecule displaces the bromide ion of a second molecule, then the reaction is an intermolecular reaction. *Inter* is Latin for "between," so an **intermolecular reaction** takes place between two molecules. If the product of this reaction subsequently reacts with a third bifunctional molecule (and then a fourth, and so on), a polymer will be formed. A polymer is a large molecule formed by linking together repeating units of small molecules (Section 15.0).

an intermolecular reaction

$$\mathrm{BrCH_2(CH_2)_{\mathit{n}}CH_2\ddot{\underset{..}{O}}{:}^-} \quad \mathrm{Br{-}CH_2(CH_2)_{\mathit{n}}CH_2\ddot{\underset{..}{O}}{:}^-} \longrightarrow \mathrm{BrCH_2(CH_2)_{\mathit{n}}CH_2\ddot{\underset{..}{O}}CH_2(CH_2)_{\mathit{n}}CH_2\ddot{\underset{..}{O}}{:}^-} + \mathrm{Br^-}$$

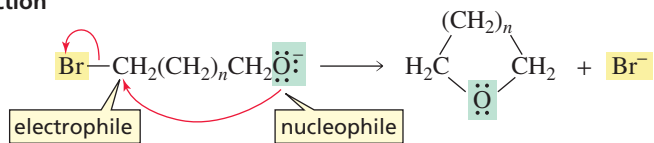
electrophile

nucleophile

Alternatively, if the alkoxide ion of a molecule displaces the bromide ion of the *same* molecule (thereby forming a cyclic compound), then the reaction is an intramolecular reaction. *Intra* is Latin for "within," so an **intramolecular reaction** takes place within a single molecule.

an intramolecular reaction

$$Br{-}CH_2(CH_2)_nCH_2\ddot{O}{:}^- \longrightarrow \text{cyclic ether } H_2C(CH_2)_nCH_2\ddot{O} + Br^-$$

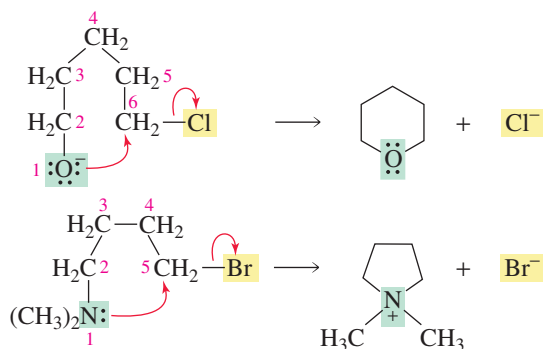
electrophile

nucleophile

Which reaction is more likely to occur, the intermolecular reaction or the intramolecular reaction? The answer depends on the *concentration* of the bifunctional molecule and the *size of the ring* that would be formed in the intramolecular reaction.

The intramolecular reaction has an advantage: the reacting groups are tethered together, so they do not have to diffuse through the solvent to find a group with which to react. (The fraction of collisions that occur with the proper orientation is greater; Section 5.8.) Therefore, a low concentration of reactant favors an intramolecular reaction because the two functional groups have a better chance of finding each other if they are in the same molecule. A high concentration of reactant helps compensate for the advantage gained by tethering, thereby increasing the likelihood of an intermolecular reaction.

How much of an advantage an intramolecular reaction has over an intermolecular reaction also depends on the size of the ring that is formed—that is, on the length of the tether. If the intramolecular reaction forms a five- or six-membered ring, then it will be favored over the intermolecular reaction because five- and six-membered rings are stable and, therefore, easily formed. (Numbering the atoms in the reactant can help you determine the size of the ring in the product.)

$$^{1}{:}\ddot{O}{:}^{-}\,{}^{2}CH_2\,{}^{3}CH_2\,{}^{4}CH_2\,{}^{5}CH_2\,{}^{6}CH_2{-}Cl \longrightarrow \text{tetrahydropyran} + Cl^-$$

$$(CH_3)_2\overset{1}{N}{:}\,{}^{2}CH_2\,{}^{3}CH_2\,{}^{4}CH_2\,{}^{5}CH_2{-}Br \longrightarrow \text{N,N-dimethylpyrrolidinium } (H_3C, CH_3, N^+) + Br^-$$

Three- and four-membered rings are strained (Section 3.10), which makes them less stable than five- and six-membered rings and, therefore, less easily formed. Therefore, the higher activation energy for formation of three- and four-membered rings cancels some of the advantage gained by tethering.

The likelihood of the reacting groups finding each other decreases sharply when the groups are in compounds that would form seven-membered and larger rings. Therefore, the intramolecular reaction becomes less favored as the ring size increases beyond six members.

PROBLEM 16♦

After a proton is removed from the OH group, which compound in each pair would form a cyclic ether more rapidly?

a. HO(CH₂)₆Br or HO(CH₂)₅Br

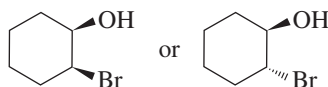
b. HO(CH₂)₄Br or HO(CH₂)₅Br

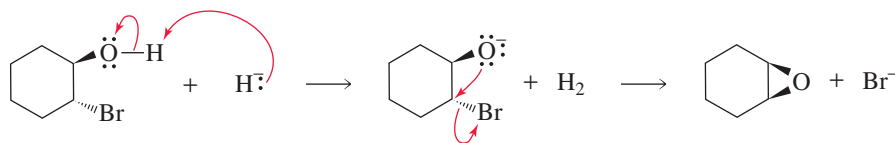
c. HO(CH₂)₆Br or HO(CH₂)₇Br

PROBLEM-SOLVING STRATEGY

Investigating How Stereochemistry Affects Reactivity

Which of the following compounds will form an epoxide as a result of reacting with sodium hydride (NaH)? An **epoxide** is an ether in which the oxygen is incorporated into a three-membered ring. (*Hint*: H^- is a strong base.)

OH / Br (cis) or OH / Br (trans)

Hydride ion will remove a proton from the OH group, forming a good nucleophile that can react with the secondary alkyl halide in an S_N2 reaction to form an epoxide. An S_N2 reaction requires back-side attack. Only when the alkoxide ion and Br are on opposite sides of the cyclohexane ring will the alkoxide ion be able to attack the back side of the carbon that is attached to Br. Therefore, only the trans isomer will be able to form an epoxide.

$\ddot{O}$—H (Br) + H:$^-$ ⟶ $\ddot{O}$:$^-$ (Br) + H_2 ⟶ O (epoxide) + Br^-

Now use the strategy you have just learned to solve Problem 17.

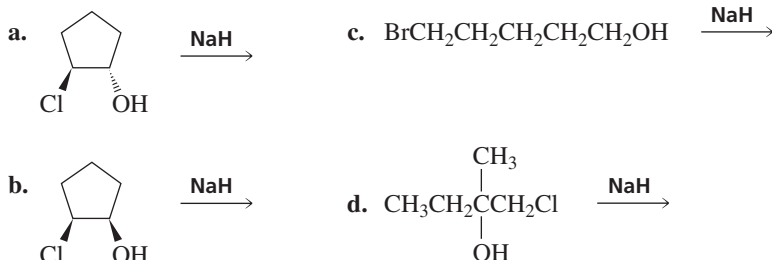
PROBLEM 17

Draw the product of each of the following intramolecular reactions:

a. (cyclopentane with Cl and OH, trans) $\xrightarrow{\text{NaH}}$

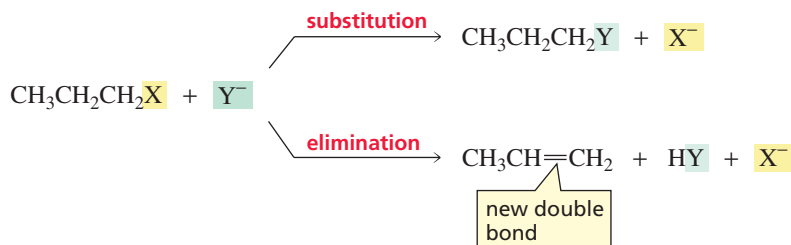
b. (cyclopentane with Cl and OH, cis) $\xrightarrow{\text{NaH}}$

c. $BrCH_2CH_2CH_2CH_2CH_2OH$ $\xrightarrow{\text{NaH}}$

d. $CH_3CH_2C(CH_3)(OH)CH_2Cl$ $\xrightarrow{\text{NaH}}$

8.7 ELIMINATION REACTIONS OF ALKYL HALIDES

In addition to undergoing nucleophilic substitution reactions, alkyl halides also undergo elimination reactions. In an **elimination reaction,** atoms or groups are removed from a reactant.

$CH_3CH_2CH_2X + Y^-$ $\xrightarrow{\text{substitution}}$ $CH_3CH_2CH_2Y + X^-$

$CH_3CH_2CH_2X + Y^-$ $\xrightarrow{\text{elimination}}$ $CH_3CH{=}CH_2 + HY + X^-$

new double bond

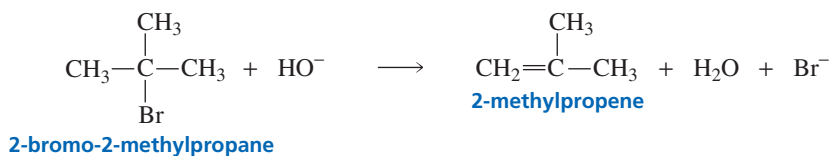
Notice that, when an alkyl halide undergoes an elimination reaction, the halogen (X) is removed from one carbon and a hydrogen is removed from an adjacent carbon. A double bond is formed between the two carbons from which the atoms are eliminated. Therefore, *the product of an elimination reaction is an alkene.*

The product of an elimination reaction is an alkene.

The E2 Reaction

Just as there are two nucleophilic substitution reactions, S_N1 and S_N2, there are two important elimination reactions, E1 and E2. The following reaction is an example of an **E2 reaction,** where "E" stands for *elimination* and "2" stands for *bimolecular* (Section 8.1).

$$CH_3-C(CH_3)(Br)-CH_3 + HO^- \longrightarrow CH_2=C(CH_3)-CH_3 + H_2O + Br^-$$

2-bromo-2-methylpropane → 2-methylpropene

The rate of an E2 reaction depends on the concentrations of both the alkyl halide and the base (in this case, hydroxide ion).

$$\textbf{rate} = k[\textbf{alkyl halide}][\textbf{base}]$$

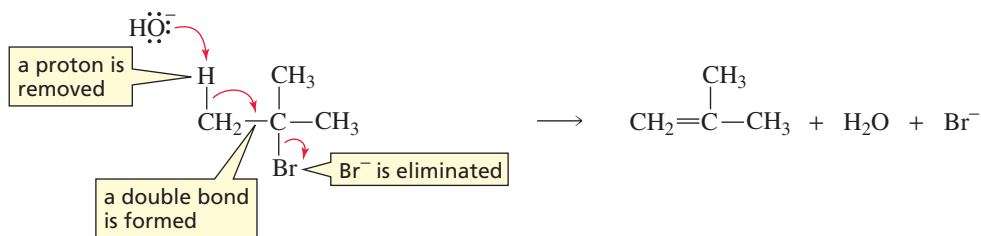
The rate law tells us that both the alkyl halide and the base are involved in the transition state of the rate-determining step, indicating a one-step reaction. The following mechanism—which portrays an E2 reaction as a one-step reaction—agrees with the observed rate law:

MECHANISM FOR THE E2 REACTION

$$HO^- + H-CH_2-C(CH_3)(Br)-CH_3 \longrightarrow CH_2=C(CH_3)-CH_3 + H_2O + Br^-$$

a proton is removed

a double bond is formed

Br^- is eliminated

- The base removes a proton from a β-carbon; a ***β*-carbon** is a carbon that is adjacent to the carbon bonded to the halogen. As the proton is removed, the electrons that it shared with carbon move toward the carbon that is bonded to the halogen. As these electrons move toward the carbon, the halogen leaves (because carbon can form no more than four bonds), taking its bonding electrons with it.

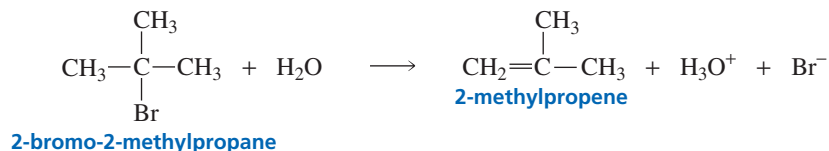
Primary, secondary, and tertiary alkyl halides undergo E2 reactions.

When the reaction is over, the electrons that were originally bonded to the hydrogen in the reactant have formed a π bond in the product. Primary, secondary, and tertiary alkyl halides can undergo E2 reactions.

The E1 Reaction

The second kind of elimination reaction that alkyl halides can undergo is an **E1 reaction,** where "E" stands for *elimination* and "1" stands for *unimolecular.*

$$CH_3-C(CH_3)(Br)-CH_3 + H_2O \longrightarrow CH_2=C(CH_3)-CH_3 + H_3O^+ + Br^-$$

2-bromo-2-methylpropane → 2-methylpropene

The rate of an E1 reaction depends only on the concentration of the alkyl halide.

$$\textbf{rate} = k[\textbf{alkyl halide}]$$

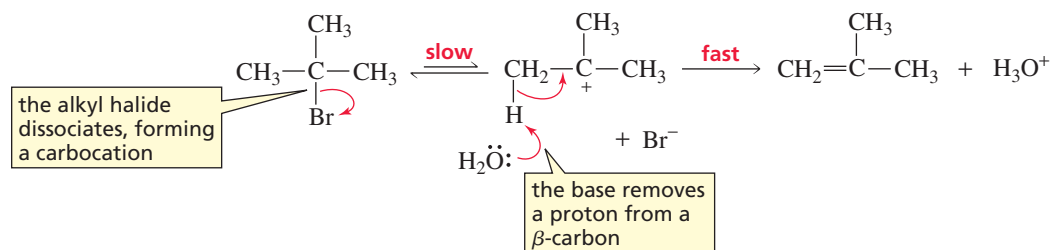
Therefore, we know that only the alkyl halide takes part in the rate-determining step of the reaction, so an E1 reaction must have at least two steps. The following mechanism agrees with the observed rate law. Because the first step is the rate-determining step, an increase in the concentration of the base—which participates only in the second step of the reaction—has no effect on the rate of the reaction.

MECHANISM FOR THE E1 REACTION

$$CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 \xrightarrow{\text{slow}} \underset{H}{CH_2}-\overset{CH_3}{\underset{+}{C}}-CH_3 + Br^- \xrightarrow{\text{fast}} CH_2=\overset{CH_3}{C}-CH_3 + H_3O^+$$

$H_2\ddot{O}:$

the alkyl halide dissociates, forming a carbocation

the base removes a proton from a β-carbon

- The alkyl halide dissociates, forming a carbocation.
- The base forms the elimination product by removing a proton from a β-carbon.

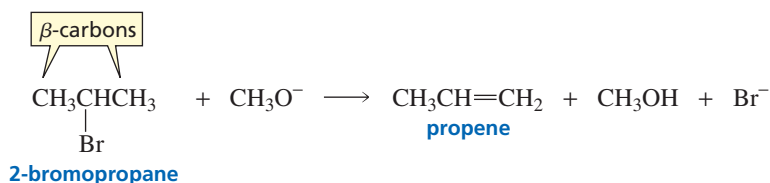
Only tertiary alkyl halides undergo E1 reactions.

Because the rate-determining step of an E1 reaction is carbocation formation, the rate of an E1 reaction depends both on the ease with which the carbocation is formed *and* on how readily the leaving group leaves. Therefore, only tertiary alkyl halides readily undergo E1 reactions. Primary and secondary alkyl halides *do not* undergo E1 reactions because their carbocations are less stable. Primary and secondary alkyl halides undergo only E2 reactions.

8.8 THE PRODUCTS OF AN ELIMINATION REACTION

In an elimination reaction, a hydrogen is removed from a β-carbon. (The halogen is bonded to the α-carbon; the β-carbon is adjacent to the α-carbon.) An alkyl halide such as 2-bromopropane has two β-carbons from which a proton can be removed in an elimination reaction. Because the two β-carbons are identical, the proton can be removed equally easily from either one.

β-carbons

$$\underset{\text{2-bromopropane}}{CH_3\underset{Br}{C}HCH_3} + CH_3O^- \longrightarrow \underset{\text{propene}}{CH_3CH=CH_2} + CH_3OH + Br^-$$

E2 and E1 Reactions Are Regioselective

2-Bromobutane has two structurally different β-carbons from which a proton can be removed. Therefore, when this alkyl halide reacts with a base, two elimination products are formed: 2-butene (80%) and 1-butene (20%). Thus, this E2 reaction is *regioselective* because more of one constitutional isomer is formed than of the other (Section 6.3).

β-carbons

$$\underset{\text{2-bromobutane}}{CH_3\underset{Br}{C}HCH_2CH_3} + CH_3O^- \longrightarrow \underset{\substack{\text{2-butene}\\80\%}}{CH_3CH=CHCH_3} + \underset{\substack{\text{1-butene}\\20\%}}{CH_2=CHCH_2CH_3} + CH_3OH + Br^-$$

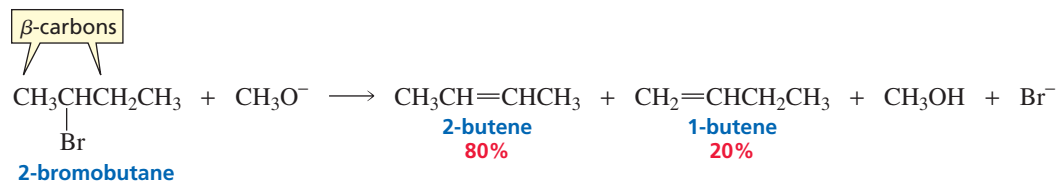
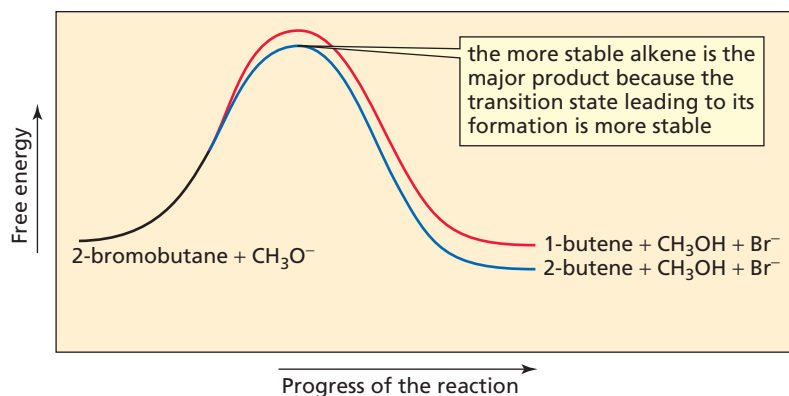
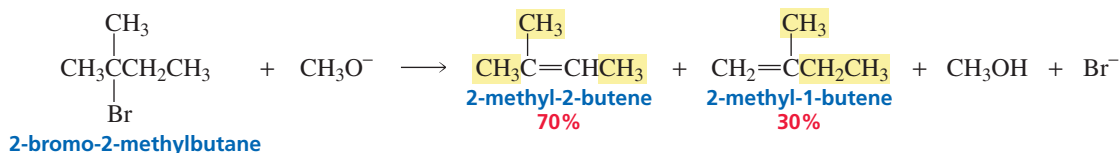
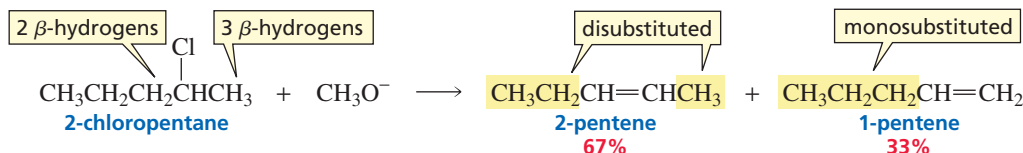



Figure 8.6 shows that the difference in the rate of formation of the two alkenes is not very great. Consequently, both are formed, but the *more stable* alkene is the major product. We have seen that the stability of an alkene depends on the number of alkyl substituents bonded to its sp^2 carbons: the greater the number of alkyl substituents, the more stable the alkene (Section 5.6). Therefore, 2-butene, with two methyl substituents bonded to its sp^2 carbons, is more stable than 1-butene, with one ethyl substituent. Thus, 2-butene is the major product.

Figure 8.6
The major product of the E2 reaction of 2-bromobutane and methoxide ion is 2-butene (indicated by the blue line), because the transition state leading to its formation is more stable than the transition state leading to formation of 1-butene (indicated by the red line).

The following reaction also forms two elimination products. Because 2-methyl-2-butene is the more substituted alkene (it has a greater number of alkyl substituents bonded to its sp^2 carbons), it is the more stable of the two alkenes and, therefore, is the major product of the elimination reaction.

$$CH_3C(CH_3)(Br)CH_2CH_3 + CH_3O^- \longrightarrow CH_3C(CH_3){=}CHCH_3 + CH_2{=}C(CH_3)CH_2CH_3 + CH_3OH + Br^-$$

2-bromo-2-methylbutane → 2-methyl-2-butene (70%) + 2-methyl-1-butene (30%)

Notice *that the more substituted alkene is obtained when a hydrogen is removed from the* β-carbon that is bonded to the fewest hydrogens. For example, in the next reaction, one β-carbon is bonded to three hydrogens and the other β-carbon is bonded to two hydrogens. The more substituted alkene will be the one formed by removing a proton from the β-carbon bonded to two hydrogens. Therefore, 2-pentene (a disubstituted alkene) is the major product and 1-pentene (a monosubstituted alkene) is the minor product.

The major product of an E2 reaction is generally the more stable alkene.

$$CH_3CH_2CH_2CH(Cl)CH_3 + CH_3O^- \longrightarrow CH_3CH_2CH{=}CHCH_3 + CH_3CH_2CH_2CH{=}CH_2$$

2-chloropentane (2 β-hydrogens; 3 β-hydrogens) → 2-pentene (disubstituted) 67% + 1-pentene (monosubstituted) 33%

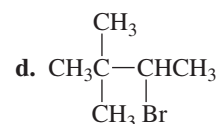
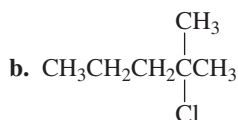
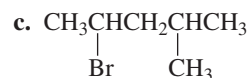
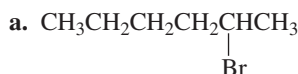
PROBLEM 18♦ Solved

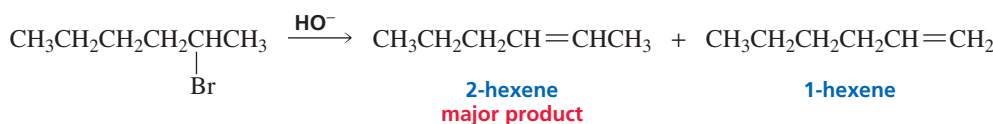
What would be the major elimination product obtained from the E2 reaction of each of the following alkyl halides with hydroxide ion?

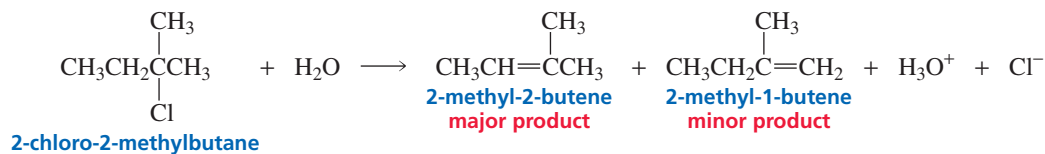
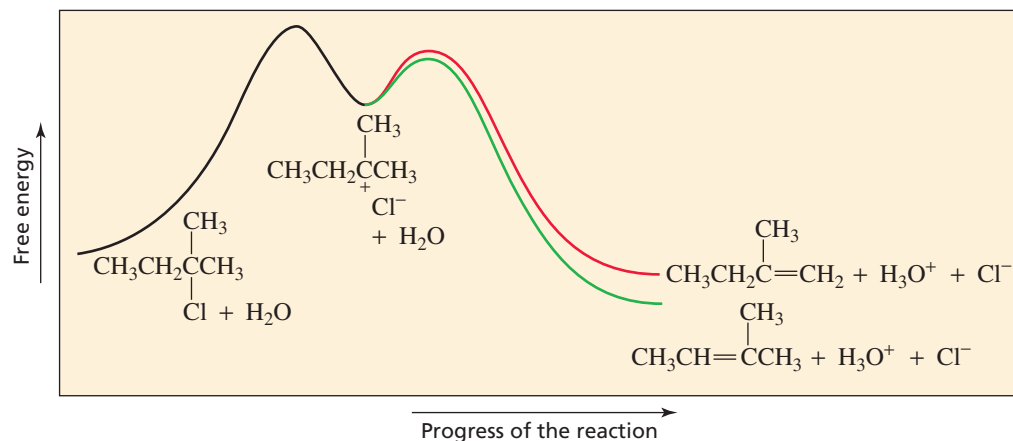
a. $CH_3CH_2CH_2CH_2CH(Br)CH_3$

b. $CH_3CH_2CH_2C(CH_3)(Cl)CH_3$

c. $CH_3CH(Br)CH_2CH(CH_3)CH_3$

d. $CH_3C(CH_3)_2{-}CH(Br)CH_3$

Solution to 18a More 2-hexene will be formed than 1-hexene, because 2-hexene is more stable since it has more alkyl substituents bonded to its sp^2 carbons.

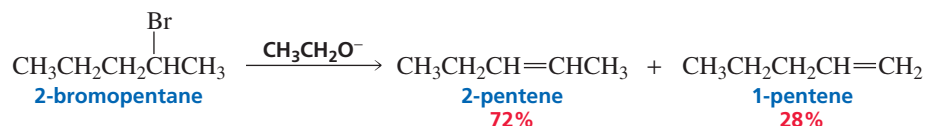
$$\underset{\underset{\text{Br}}{|}}{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCH}_3} \xrightarrow{\text{HO}^-} \underset{\substack{\textbf{2-hexene}\\ \textbf{major product}}}{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}{=}\text{CHCH}_3} + \underset{\textbf{1-hexene}}{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}{=}\text{CH}_2}$$

When more than one alkene can be formed, the E1 reaction, like the E2 reaction, is regioselective. And, as in the E2 reaction, the major product is the *more stable alkene.*

$$\underset{\textbf{2-chloro-2-methylbutane}}{\text{CH}_3\text{CH}_2\overset{\text{CH}_3}{\underset{\text{Cl}}{\text{C}}}\text{CH}_3} + \text{H}_2\text{O} \longrightarrow \underset{\substack{\textbf{2-methyl-2-butene}\\ \textbf{major product}}}{\text{CH}_3\text{CH}{=}\overset{\text{CH}_3}{\text{C}}\text{CH}_3} + \underset{\substack{\textbf{2-methyl-1-butene}\\ \textbf{minor product}}}{\text{CH}_3\text{CH}_2\overset{\text{CH}_3}{\text{C}}{=}\text{CH}_2} + \text{H}_3\text{O}^+ + \text{Cl}^-$$

The more stable alkene is the major product because its greater stability causes the transition state leading to its formation to be more stable (Figure 8.7). Therefore, it is formed more rapidly. Notice that, as we have seen in the E2 reaction, the more stable alkene is formed by removing the hydrogen from the β-carbon bonded to the fewest hydrogens.

▲ **Figure 8.7**
The major product of the E1 reaction is the more stable alkene (green line) because its greater stability causes the transition state leading to its formation to be more stable.

E2 and E1 Reactions Are Stereoselective

We have just seen that E2 and E1 reactions are *regioselective,* meaning that more of one *constitutional isomer* is formed than the other. E2 and E1 reactions are also stereoselective. A **stereoselective reaction** is a reaction that forms more of one *stereoisomer* than of another.

For example, we know that the major product of the following E2 reaction is 2-pentene because 2-pentene is more stable than 1-pentene (Section 8.8).

$$\underset{\textbf{2-bromopentane}}{\text{CH}_3\text{CH}_2\text{CH}_2\overset{\text{Br}}{\text{C}}\text{HCH}_3} \xrightarrow{\text{CH}_3\text{CH}_2\text{O}^-} \underset{\substack{\textbf{2-pentene}\\ \textbf{72\%}}}{\text{CH}_3\text{CH}_2\text{CH}{=}\text{CHCH}_3} + \underset{\substack{\textbf{1-pentene}\\ \textbf{28\%}}}{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}{=}\text{CH}_2}$$

However, the major product of this E2 reaction (2-pentene) has two stereoisomers, (*E*)-2-pentene and (*Z*)-2-pentene. The reaction forms more (*E*)-2-pentene than (*Z*)-2-pentene, because (*E*)-2-pentene is more stable. Recall that the more stable stereoisomer is the one with the largest groups on opposite sides of the double bond because it has less steric strain (Section 5.6).

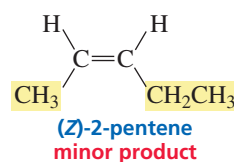
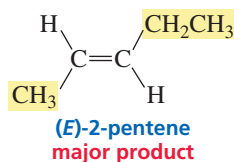
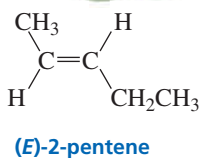
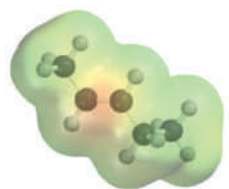
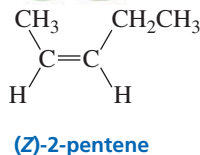
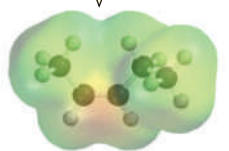
$CH_3(H)C{=}C(H)CH_2CH_3$ (cis)

(Z)-2-pentene

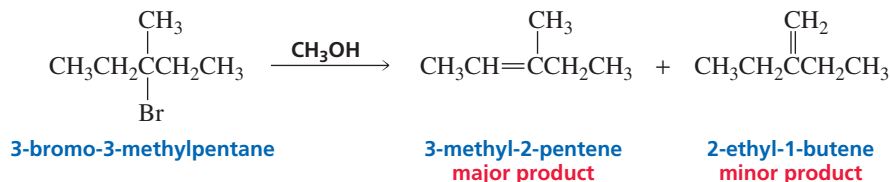
$CH_3(H)C{=}C(H)CH_2CH_3$ (trans)

(E)-2-pentene

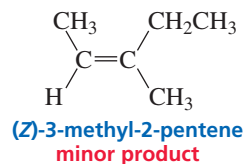
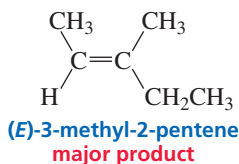
$CH_3(H)C{=}C(H)CH_2CH_3$ — **(E)-2-pentene**, major product

$CH_3(H)C{=}C(H)CH_2CH_3$ — **(Z)-2-pentene**, minor product

E1 reactions are also stereoselective in addition to being regioselective. For example, the major product of the following reaction is 3-methyl-2-pentene, because it is the more stable of the two *constitutional isomers*.

$$CH_3CH_2C(CH_3)(Br)CH_2CH_3 \xrightarrow{CH_3OH} CH_3CH{=}C(CH_3)CH_2CH_3 + CH_3CH_2C({=}CH_2)CH_2CH_3$$

3-bromo-3-methylpentane → **3-methyl-2-pentene** (major product) + **2-ethyl-1-butene** (minor product)

The major product, 3-methyl-2-pentene, can exist as stereoisomers. More (*E*)-3-methyl-2-pentene is formed than (*Z*)-3-methyl-2-pentene, because the former is the more stable *stereoisomer* since the largest groups are on opposite sides of the double bond.

$CH_3(H)C{=}C(CH_3)CH_2CH_3$ — **(E)-3-methyl-2-pentene**, major product

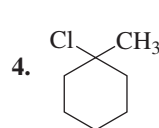
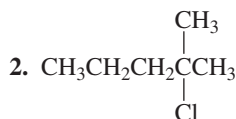
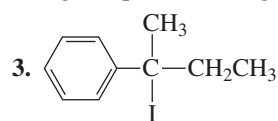
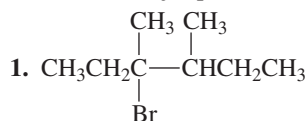
$CH_3(H)C{=}C(CH_2CH_3)CH_3$ — **(Z)-3-methyl-2-pentene**, minor product

PROBLEM 19♦ Solved

a. What is the major product formed when the following compounds undergo an E1 reaction?

1. $CH_3CH_2C(CH_3)(Br){-}CH(CH_3)CH_2CH_3$

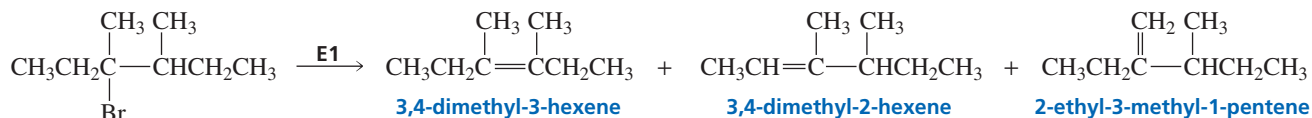
2. $CH_3CH_2CH_2C(CH_3)(Cl)CH_3$

3. $C_6H_5{-}C(CH_3)(I){-}CH_2CH_3$

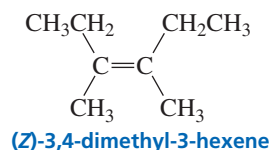
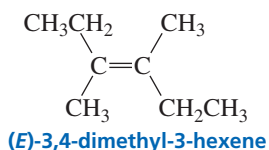
4. 1-chloro-1-methylcyclohexane (Cl and CH_3 on the same ring carbon)

b. What is the major product formed when the compounds undergo an E2 reaction?

Solution to 19a (1) First, we need to consider the *regiochemistry* of the reaction: the major product will be 3,4-dimethyl-3-hexene because it is the most stable of the three possible alkene products.

$$CH_3CH_2C(CH_3)(Br){-}CH(CH_3)CH_2CH_3 \xrightarrow{E1} CH_3CH_2C(CH_3){=}C(CH_3)CH_2CH_3 + CH_3CH{=}C(CH_3){-}CH(CH_3)CH_2CH_3 + CH_3CH_2C({=}CH_2){-}CH(CH_3)CH_2CH_3$$

3,4-dimethyl-3-hexene + **3,4-dimethyl-2-hexene** + **2-ethyl-3-methyl-1-pentene**

Next, we need to consider the *stereochemistry* of the reaction: the major product has two stereoisomers and more (*E*)-3,4-dimethyl-3-hexene will be formed because it is more stable than (*Z*)-3,4-dimethyl-3-hexene. Thus, (*E*)-3,4-dimethyl-3-hexene is the major product of the reaction.

$CH_3CH_2(CH_3)C{=}C(CH_3)CH_2CH_3$ — **(E)-3,4-dimethyl-3-hexene**

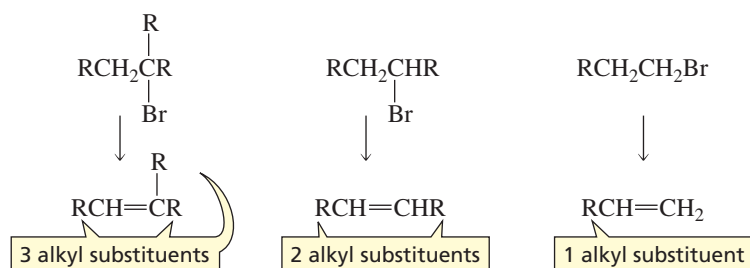
$CH_3CH_2(CH_3)C{=}C(CH_3)CH_2CH_3$ — **(Z)-3,4-dimethyl-3-hexene**

Solution to 19b (1) The compound that is the major product in an E2 reaction is also the major product in an E1 reaction, because both E2 and E1 are regioselective and stereoselective.

8.9 RELATIVE REACTIVITIES OF ALKYL HALIDES REACTIONS

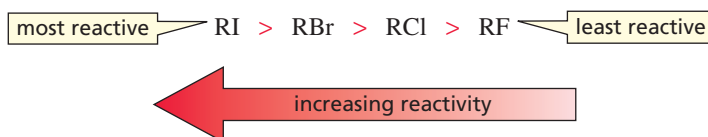
Primary, secondary, and tertiary alkyl halides are all able to undergo E2 reactions. (Recall that only tertiary alkyl halides can undergo E1 reactions.)

Because elimination from a tertiary alkyl halide typically leads to a more substituted alkene than does elimination from a secondary alkyl halide, and because elimination from a secondary alkyl halide generally leads to a more substituted alkene than does elimination from a primary alkyl halide, the relative reactivities of alkyl halides in an E2 reaction are:

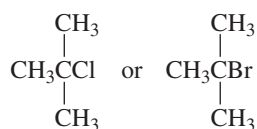
relative reactivities of alkyl halides in an E2 reaction

tertiary alkyl halide > secondary alkyl halide > primary alkyl halide

For a series of alkyl halides with the same alkyl group, alkyl iodides are the most reactive and alkyl fluorides are the least reactive in both E2 and E1 reactions, because weaker bases are better leaving groups (Sections 8.2 and 8.4).

The weaker the base, the better it is as a leaving group.

relative reactivities of alkyl halides in E2 and E1 reactions

PROBLEM 20♦

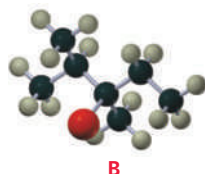
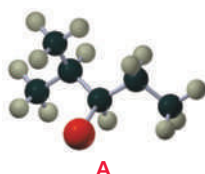
a. Which alkyl halide would you expect to be more reactive in an E2 reaction?
b. Which would be more reactive in an E1 reaction?

$$(CH_3)_2CClCH_3 \quad \text{or} \quad (CH_3)_2CBrCH_3$$

PROBLEM 21♦

Which of the following compounds would react faster in an

a. E1 reaction? **b.** E2 reaction? **c.** S_N1 reaction? **d.** S_N2 reaction?

A

B

The Nobel Prize

The Nobel Prize is generally considered the highest honor a scientist can receive. These awards were established by **Alfred Bernhard Nobel (1833–1896)** and were first conferred in 1901.

Nobel was born in Stockholm, Sweden. When he was nine, he moved with his parents to St. Petersburg, Russia, where his father worked for the Russian government, manufacturing torpedoes and land and water mines that he had invented. As a young man, Alfred did research on explosives in a factory his father owned near Stockholm. In 1864, an explosion in the factory killed five people, including his younger brother, causing Alfred to look for ways to make explosives easier to handle and transport. After the explosion, the Swedish government would not allow the factory to be rebuilt because so many accidents had occurred there. Nobel, therefore, established an explosives factory in Germany, where, in 1867, he discovered that nitroglycerin mixed with diatomaceous earth can be molded into sticks that cannot be set off without a detonating cap. Thus, Nobel invented dynamite. He also invented blasting gelatin and smokeless powder. Although he was the inventor of the explosives used by the military, he was a strong supporter of peace movements.

Alfred Bernhard Nobel

The Golden Hall inside the City Hall in Stockholm, where the Nobel prize winners have a celebratory dinner.

The 355 patents Nobel held made him a wealthy man. He never married, and when he died, his will stipulated for the bulk of his estate ($9,200,000) to be used to establish prizes to be awarded to those who "have conferred the greatest benefit on mankind." He instructed that the money be invested and the interest earned each year be divided into five equal portions "to be awarded to the persons having made the most important contributions in the fields of chemistry, physics, physiology or medicine, literature, and to the one who had done the most toward fostering fraternity among nations, the abolition of standing armies, and the holding and promotion of peace congresses." Nobel also directed that no consideration be given to the nationality of the prize candidates, that each prize be shared by no more than three persons, and that no prize be awarded posthumously.

Nobel's instructions said that the prizes for chemistry and physics were to be awarded by the Royal Swedish Academy of Sciences, the prizes for physiology or medicine by the Karolinska Institute in Stockholm, the prize for literature by the Swedish Academy, and the prize for peace by a five-person committee appointed by the Norwegian Parliament. The deliberations are secret, and the decisions cannot be appealed. In 1969, the Swedish Central Bank established a prize in economics in Nobel's honor. The recipient of this prize is selected by the Royal Swedish Academy of Sciences. On December 10—the anniversary of Nobel's death—the prizes are awarded in Stockholm, except for the peace prize, which is awarded in Oslo.

8.10 DOES A TERTIARY ALKYL HALIDE UNDERGO S_N2/E2 REACTIONS OR S_N1/E1 REACTIONS?

When carrying out a reaction of a tertiary alkyl halide, it is important to know whether the reaction conditions will cause S_N2 and E2 reactions to occur or will cause S_N1 and E1 reactions to occur.

Recall that tertiary alkyl halides undergo E2 reactions and S_N1 and E1 reactions (also recall that they are too sterically hindered to undergo S_N2 reactions). Therefore, if the reaction conditions favor S_N2 and E2 reactions, only an elimination product will be formed. On the other hand, if the reaction conditions favor S_N1 and E1 reactions, both substitution and elimination products will be formed. Notice, in the following discussion, that HO^- is called a nucleophile in a substitution reaction (because it attacks a carbon) and it is called a base in an elimination reaction (because it removes a proton).

Two factors determine whether S_N2/E2 or S_N1/E1 reactions predominate: (1) the *concentration* of the nucleophile/base and (2) the *reactivity* of the nucleophile/base. To understand how these two factors determine the set of reactions that predominates, we must look at the overall rate law for the reaction. The overall rate law is the sum of the individual rate laws for the S_N1, S_N2, E1, and E2 reactions. (Subscripts have been added to the rate constants to indicate that they have different values.)

From the overall rate law, you can see that increasing the *concentration* of the nucleophile/base has no effect on the rate of the S_N1 and E1 reactions, because the concentration of the nucleophile/base is not in their rate laws. In contrast, increasing the *concentration* of the nucleophile/base increases the rate of the S_N2 and E2 reactions, because the concentration of the nucleophile/base is in their rate laws. Similarly, increasing the *reactivity* of the nucleophile/base has no effect on the rate of S_N1 and E1 reactions, because the slow step in these reactions does not involve the nucleophile/base. It does, however, increase the rate of the S_N2 and E2 reactions by increasing the value of their rate constants (k_2 and k_4), because a more reactive nucleophile/base is better able to displace the leaving group. In summary:

- S_N2 and E2 reactions are favored by a high concentration of a good nucleophile/strong base.
- S_N1 and E1 reactions are favored by a poor nucleophile/weak base because a poor nucleophile/weak base disfavors S_N2 and E2 reactions.

Recall that primary and secondary alkyl halides do not undergo S_N1/E1 solvoylsis reactions. Even though the nucleophile/base is weak, presumably its high concentration (since it is the solvent), causes S_N2/E2 reactions to predominate.

Therefore, the only time we have to determine whether the reaction conditions favor S_N2/E2 or S_N1/E1 reactions is when the alkyl halide is tertiary.

8.11 COMPETITION BETWEEN SUBSTITUTION AND ELIMINATION

Now we need to determine whether an alkyl halide will form a substitution product, an elimination product, or both substitution and elimination products. The answer will depend on the structure of the alkyl halide (that is, whether it is primary, secondary, or tertiary).

S_N2/E2 Conditions

S_N2/E2 reactions compete with each other. For example, the following reactions show that hydroxide ion can act as a nucleophile and attack the back side of the α-carbon to form the substitution product, or it can act as a base and remove a hydrogen from a β-carbon to form the elimination product.

$$CH_3{-}CH_2{-}Br \longrightarrow CH_3CH_2OH + Br^-$$

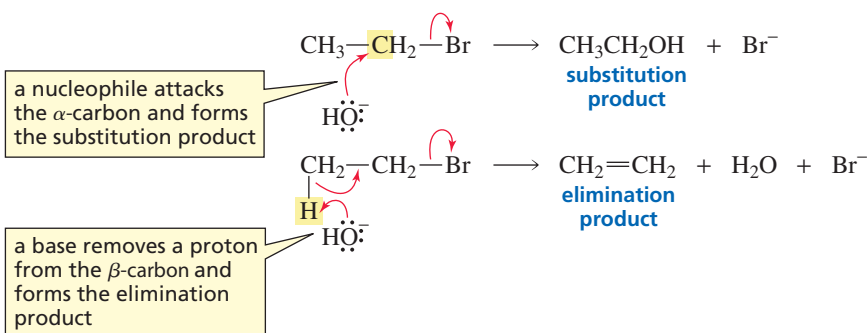
substitution product

a nucleophile attacks the α-carbon and forms the substitution product

HO^-

$$CH_2(H){-}CH_2{-}Br \longrightarrow CH_2{=}CH_2 + H_2O + Br^-$$

elimination product

a base removes a proton from the β-carbon and forms the elimination product

The relative reactivities of alkyl halides in S_N2 and E2 reactions are shown here:

In an S_N2 reaction: $1° > 2° > 3°$ **In an E2 reaction:** $3° > 2° > 1°$

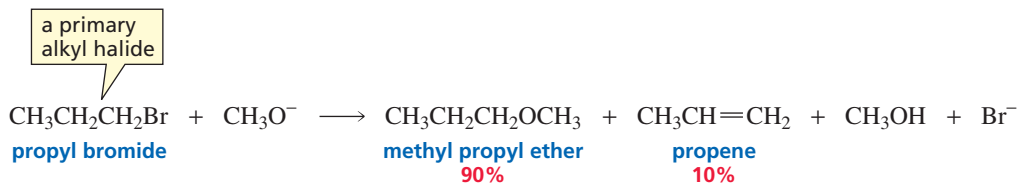
Primary alkyl halides undergo primarily substitution under S_N2/E2 conditions.

Primary Alkyl Halides

Because a *primary* alkyl halide is the most reactive in an S_N2 reaction (the back side of the α-carbon is relatively unhindered; Section 8.1) and the least reactive in an E2 reaction (Section 8.9), a primary alkyl halide forms principally the substitution product. In other words, substitution wins the competition.

a primary alkyl halide

$$CH_3CH_2CH_2Br + CH_3O^- \longrightarrow CH_3CH_2CH_2OCH_3 + CH_3CH{=}CH_2 + CH_3OH + Br^-$$

propyl bromide → methyl propyl ether 90% ; propene 10%

Secondary alkyl halides undergo substitution and elimination under S_N2/E2 conditions.

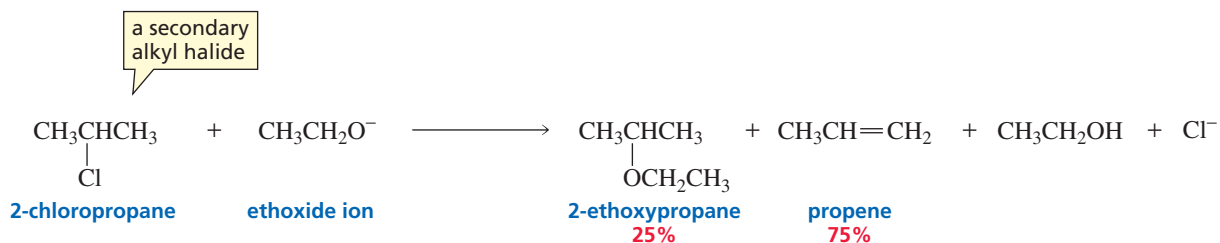
Secondary Alkyl Halides

A *secondary* alkyl halide, compared with a primary alkyl halide, reacts slower in an S_N2 reaction and faster in an E2 reaction. Thus, a *secondary* alkyl halide forms both substitution and elimination products.

a secondary alkyl halide

$$CH_3CH(Cl)CH_3 + CH_3CH_2O^- \longrightarrow CH_3CH(OCH_2CH_3)CH_3 + CH_3CH{=}CH_2 + CH_3CH_2OH + Cl^-$$

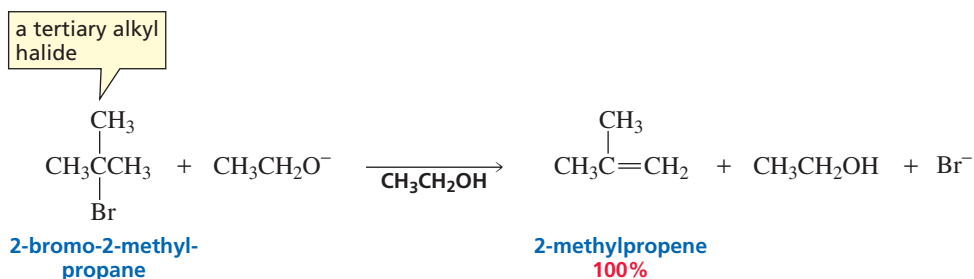
2-chloropropane + ethoxide ion → 2-ethoxypropane 25% ; propene 75%

Tertiary alkyl halides undergo only elimination under S_N2/E2 conditions.

Tertiary Alkyl Halides

A *tertiary* alkyl halide cannot undergo an S_N2 reaction. Consequently, *only the elimination product* is formed when a tertiary alkyl halide reacts with a nucleophile/base under S_N2/E2 conditions.

a tertiary alkyl halide

$$CH_3C(CH_3)(Br)CH_3 + CH_3CH_2O^- \xrightarrow{CH_3CH_2OH} CH_3C(CH_3){=}CH_2 + CH_3CH_2OH + Br^-$$

2-bromo-2-methylpropane → 2-methylpropene 100%

S_N1/E1 Conditions

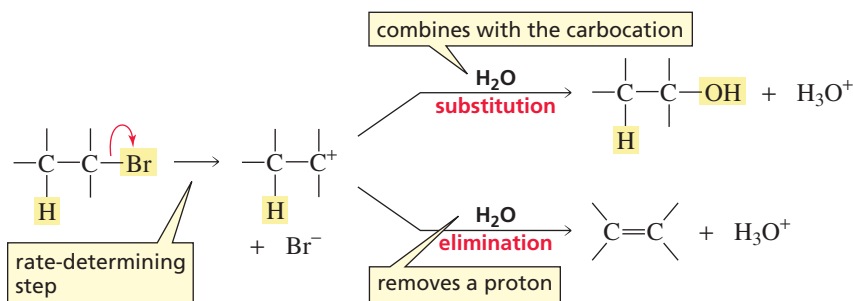
Recall that in S_N1/E1 reactions, the alkyl halide dissociates to form a carbocation, which can then either combine with the nucleophile to form the substitution product or lose a proton to form the elimination product.

Tertiary alkyl halides undergo substitution and elimination reactions under S_N1/E1 conditions.

$$-\overset{|}{\underset{H}{C}}-\overset{|}{\underset{|}{C}}-Br \longrightarrow -\overset{|}{\underset{H}{C}}-\overset{|}{\underset{|}{C^+}} + Br^-$$

rate-determining step

combines with the carbocation: $\xrightarrow[\text{substitution}]{H_2O}$ $-\overset{|}{\underset{H}{C}}-\overset{|}{\underset{|}{C}}-OH + H_3O^+$

removes a proton: $\xrightarrow[\text{elimination}]{H_2O}$ $>C{=}C< + H_3O^+$

S_N1 and E1 reactions both have the same rate-determining step—dissociation of the alkyl halide to form a carbocation. This means that any alkyl halide that reacts under S_N1/E1 conditions will form both substitution and elimination products.

It is fortunate that the S_N1/E1 reactions of tertiary alkyl halides favor the substitution product, because under S_N2/E2 conditions only the elimination product is formed.

$$(CH_3)_3CBr + CH_3CH_2OH \xrightarrow[\text{conditions}]{S_N1/E1} \underset{81\%}{(CH_3)_3COCH_2CH_3} + \underset{19\%}{CH_3C(CH_3){=}CH_2}$$

$$(CH_3)_3CBr + CH_3CH_2O^- \xrightarrow[\text{conditions}]{S_N2/E2} \underset{100\%}{CH_3C(CH_3){=}CH_2}$$

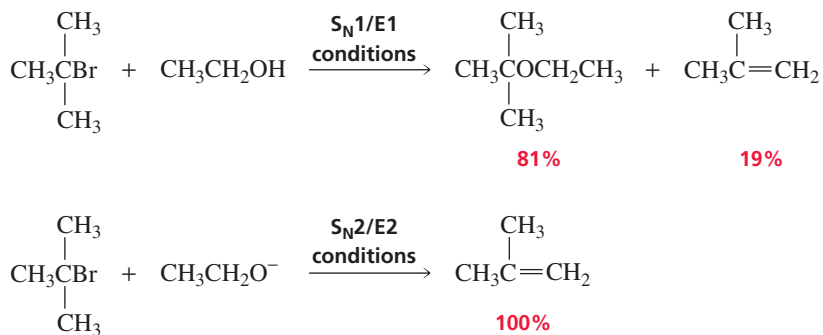



Table 8.2 Summary of the Products Expected in Substitution and Elimination Reactions

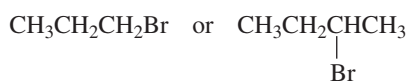
Class of alkyl halide	S_N2 versus E2	S_N1 versus E1
Primary alkyl halide	primarily substitution	cannot undergo S_N1/E1 solvoylsis reactions
Secondary alkyl halide	substitution and elimination	cannot undergo S_N1/E1 solvolysis reactions
Tertiary alkyl halide	only elimination	substitution and elimination with substitution favored

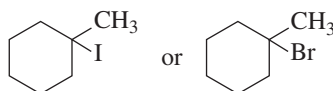
PROBLEM 22

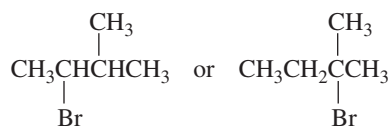
Why do the S_N1/E1 reactions of tertiary alkyl halides favor the substitution product?

PROBLEM 23♦

a. Which reacts faster in an S_N2 reaction?

$CH_3CH_2CH_2Br$ or $CH_3CH_2CH(Br)CH_3$

b. Which reacts faster in an E1 reaction?

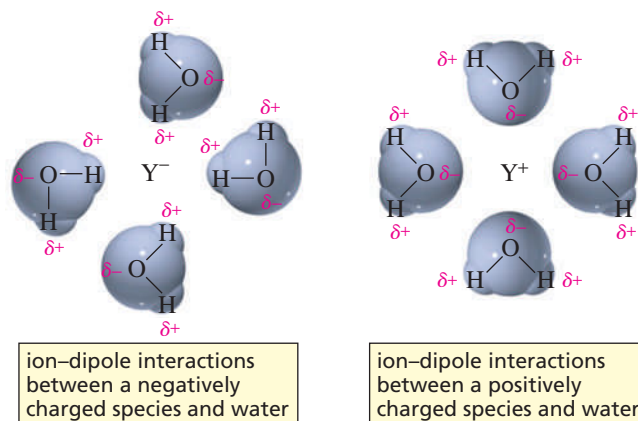
1-iodo-1-methylcyclohexane (CH$_3$, I) or 1-bromo-1-methylcyclohexane (CH$_3$, Br)

c. Which reacts faster in an S_N1 reaction?

$CH_3CH(Br)CH(CH_3)CH_3$ or $CH_3CH_2C(CH_3)(Br)CH_3$

PROBLEM 24♦

Indicate whether the specified alkyl halides will form primarily substitution products, only elimination products, both substitution and elimination products, or no products when they react with sodium methoxide.

a. 1-bromobutane
b. 1-bromo-2-methylpropane
c. 2-bromobutane
d. 2-bromo-2-methylpropane

8.12 SOLVENT EFFECTS

Polar solvents such as water and alcohols cluster around ions with the positive poles of the solvent molecules surrounding negative charges and the negative poles of the solvent molecules surrounding positive charges. Recall that the interaction between a solvent and an ion or a molecule dissolved in that solvent is called *solvation* (Section 3.7).

When an ion interacts with a polar solvent, the charge is no longer localized solely on the ion, but is spread out to the surrounding solvent molecules. Spreading out the charge stabilizes the charged species.

The stabilization of charges by solvent interaction plays an important role in organic reactions. For example, when an alkyl halide undergoes an S_N1 reaction, the first step is dissociation of the carbon–halogen bond to form a carbocation and a halide ion. Energy is required to break the bond, but with no bonds being formed, where does the energy come from? If the reaction is carried out in a polar solvent, the ions that are produced are solvated. The energy associated with a single ion–dipole interaction is small, but the additive effect of all the ion–dipole interactions that take place when a solvent stabilizes a charged species represents a great deal of energy. These ion–dipole interactions provide much of the energy necessary for dissociation of the carbon–halogen bond. So, the alkyl halide does not fall apart spontaneously in an S_N1 reaction—polar solvent molecules pull it apart. An S_N1 reaction, therefore, cannot take place in a nonpolar solvent.

Solvation Effects

The tremendous amount of energy provided by solvation can be appreciated by considering the energy required to break the crystal lattice of sodium chloride (table salt). In the absence of a solvent, sodium chloride must be heated to more than 800 °C to overcome the forces that hold the oppositely charged ions together. However, sodium chloride readily dissolves in water at room temperature because solvation of the Na^+ and Cl^- ions by water molecules provides the energy necessary to separate the ions.

How a Solvent Affects Reaction Rates in General

How increasing the polarity of the solvent will affect the rate of most chemical reactions depends *only* on whether or not a reactant that participates in the rate-limiting step is charged:

> *If a reactant that participates in the rate-determining step is charged, increasing the polarity of the solvent will decrease the rate of the reaction.*
>
> *If none of the reactants that participates in the rate-determining step is charged, increasing the polarity of the solvent will increase the rate of the reaction.*

Now let's see why this is true. The rate of a reaction depends on the difference between the free energy of the reactants and the free energy of the transition state of the rate-determining step. We can predict, therefore, how increasing the polarity of the solvent will affect the rate of a reaction simply by looking at the reactants and the transition state of the rate-determining step to see which will be more stabilized by a more polar solvent.

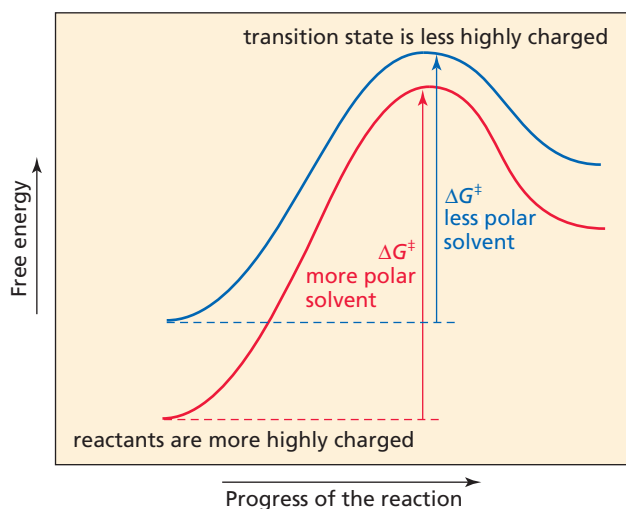
The greater or the more concentrated the charge on a molecule, the stronger will be its interactions with a polar solvent and the more the charge will be stabilized. Therefore, if the size or concentration of the charge on the reactants is greater than that on the transition state, then a polar solvent will stabilize the reactants more than it will stabilize the transition state. Therefore, *increasing the polarity of the solvent* will increase the difference in energy ($\Delta G^{\ddagger}$) between the transition state and the reactants, which *will decrease the rate of the reaction*, as shown in Figure 8.8.

Increasing the polarity of the solvent will decrease the rate of the reaction if a reactant in the rate-determining step is charged.

Figure 8.8
The charge on the reactants is greater than the charge on the transition state. As a result, increasing the polarity of the solvent increases the stability of the reactants more than the stability of the transition state, so the reaction will be slower.

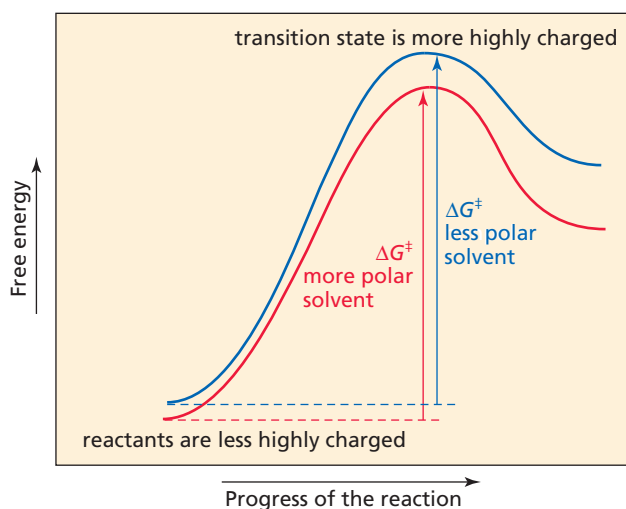
On the other hand, if the size of the charge on the transition state is greater than the size of the charge on the reactants, then a polar solvent will stabilize the transition state more than it will stabilize the reactants. Therefore, *increasing the polarity of the solvent* will decrease the difference in energy ($\Delta G^{\ddagger}$) between the transition state and the reactants, which *will increase the rate of the reaction*, as shown in Figure 8.9.

Increasing the polarity of the solvent will increase the rate of the reaction if none of the reactants in the rate-determining step is charged.

Figure 8.9
The charge on the transition state is greater than the charge on the reactants. As a result, increasing the polarity of the solvent increases the stability of the transition state more than the stability of the reactants, so the reaction will be faster.

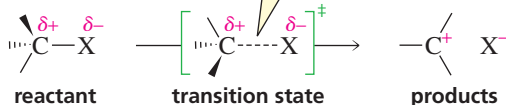
How a Solvent Affects the Rate of an S_N1 or E1 Reaction of an Alkyl Halide

Now let's look at specific reactions, beginning with an S_N1 or E1 reaction of an alkyl halide. The alkyl halide, which is the only reactant in the rate-determining step of an S_N1 or E1 reaction, is a neutral molecule with a small dipole moment. The transition state for the rate-determining step of an S_N1 or E1 reaction has greater partial charges because as the carbon–halogen bond breaks, the carbon becomes more positive and the halogen becomes more negative. Since the partial charges in the transition state are greater than the partial charges in the reactant, increasing the polarity of the solvent will stabilize

the transition state more than the reactant, which will increase the rate of the S_N1 or E1 reaction (Figure 8.9).

rate-determining step of an S_N1 or E1 reaction

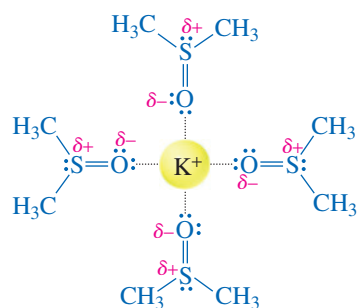
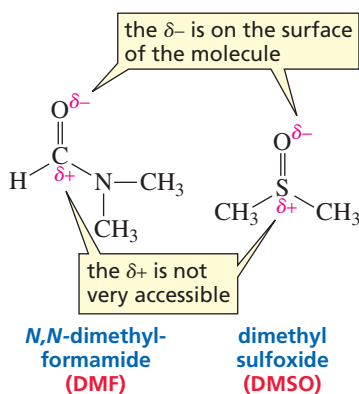
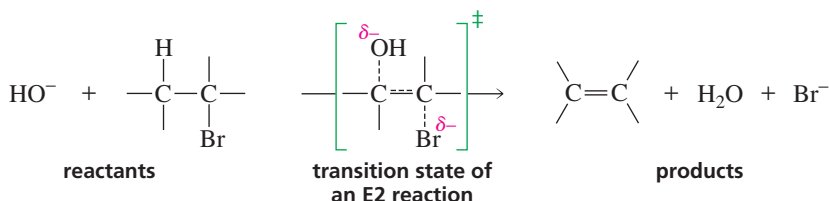
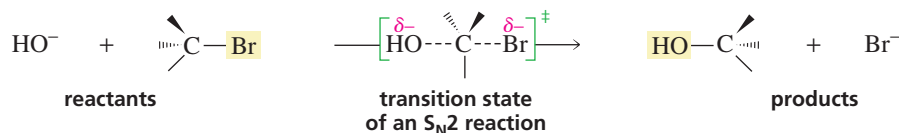
the charge on the transition state is greater than the charge on the reactants

reactant　　transition state　　products

How a Solvent Affects the Rate of an S_N2 or E2 Reaction of an Alkyl Halide

How increasing the polarity of the solvent affects the rate of an S_N2 or E2 reaction of an alkyl halide depends on whether the nucleophile/base is charged or neutral.

Most S_N2 or E2 reactions of alkyl halides occur with a charged nucleophile/base. Increasing the polarity of a solvent will have a strong stabilizing effect on the negatively charged nucleophile/base. The transition state of an S_N2 or E2 reaction also has a negative charge, but that charge is dispersed over two atoms. Consequently, the interactions between the solvent and the transition state are not as strong as those between the solvent and the fully charged nucleophile. Therefore, increasing the polarity of the solvent will stabilize the nucleophile more than it will stabilize the transition state, so the reaction will be slower (Figure 8.8).

reactants　　transition state of an S_N2 reaction　　products

reactants　　transition state of an E2 reaction　　products

DMSO can solvate a cation better than it can solvate an anion

In summary, the way a change in the polarity of the solvent affects the rate of a reaction does not depend on the mechanism of the reaction. It depends *only* on whether or not the reactants that participate in the rate-determining step are charged or neutral.

Because a polar solvent decreases the rate of an S_N2 or E2 reaction when the nucleophile is negatively charged, we would like to carry out such a reaction in a nonpolar solvent. However, negatively charged nucleophiles will not dissolve in a nonpolar solvent such as hexane. Instead, a solvent such as DMF or DMSO is used. Because they are not hydrogen bond donors, they are less effective than solvents such as water and alcohols at solvating negative charges; indeed, DMSO and DMF solvate negative charges very poorly because their partial positive charge is on the inside of the molecule.

PROBLEM 25♦

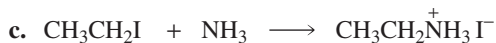
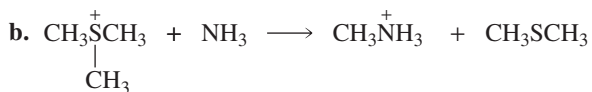
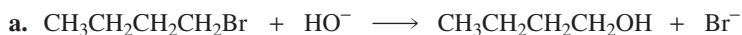
Amines are good nucleophiles, even though they are neutral molecules. How would the rate of an S_N2 reaction between an amine and an alkyl halide be affected if the polarity of the solvent is increased?

PROBLEM 26♦

How will the rate of each of the following S_N2 reactions change if it is carried out in a more polar solvent?

a. $CH_3CH_2CH_2CH_2Br + HO^- \longrightarrow CH_3CH_2CH_2CH_2OH + Br^-$

b. $CH_3\overset{+}{S}(CH_3)CH_3 + NH_3 \longrightarrow CH_3\overset{+}{N}H_3 + CH_3SCH_3$

c. $CH_3CH_2I + NH_3 \longrightarrow CH_3CH_2\overset{+}{N}H_3\ I^-$

An S_N2 reaction of an alkyl halide is favored by a high concentration of a good (negatively charged) nucleophile in an aprotic polar solvent or by a high concentration of a good (neutral) nucleophile in a protic polar solvent.

PROBLEM 27♦

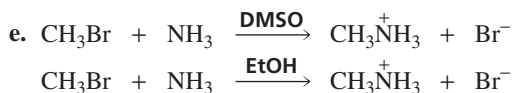
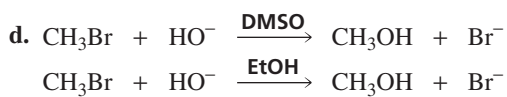
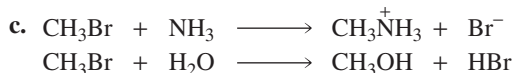
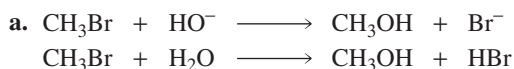
Which reaction in each of the following pairs will take place more rapidly?

a. $CH_3Br + HO^- \longrightarrow CH_3OH + Br^-$
$CH_3Br + H_2O \longrightarrow CH_3OH + HBr$

b. $CH_3I + HO^- \longrightarrow CH_3OH + I^-$
$CH_3Cl + HO^- \longrightarrow CH_3OH + Cl^-$

c. $CH_3Br + NH_3 \longrightarrow CH_3\overset{+}{N}H_3 + Br^-$
$CH_3Br + H_2O \longrightarrow CH_3OH + HBr$

d. $CH_3Br + HO^- \xrightarrow{\text{DMSO}} CH_3OH + Br^-$
$CH_3Br + HO^- \xrightarrow{\text{EtOH}} CH_3OH + Br^-$

e. $CH_3Br + NH_3 \xrightarrow{\text{DMSO}} CH_3\overset{+}{N}H_3 + Br^-$
$CH_3Br + NH_3 \xrightarrow{\text{EtOH}} CH_3\overset{+}{N}H_3 + Br^-$

An S_N1 reaction of an alkyl halide is favored by a poor nucleophile in a protic polar solvent.

PROBLEM 28 Solved

Most of the pK_a values given in this text have been determined in water. How would the pK_a value of a carboxylic acid change if it were determined in a solvent less polar than water?

Solution A pK_a is the negative logarithm of an equilibrium constant, K_a (Section 2.2). Because we are determining how decreasing the polarity of a solvent affects an equilibrium constant, we must look at how decreasing the polarity of the solvent affects the stability of the reactants and products (Section 5.4).

$$K_a = \frac{[B^-][H^+]}{[HB]}$$

a neutral acid

A carboxylic acid is neutral in its acidic form (HB) and charged in its basic form (B^-). Water will stabilize B^- and H^+ more than it will stabilize HB, thereby increasing K_a, so it will be a stronger acid in water than in a less polar solvent. Because a carboxylic acid will be a weaker acid in a less polar solvent, its pK_a value will be larger.

A carboxylic acid will be a weaker acid in a solvent that is less polar than water.

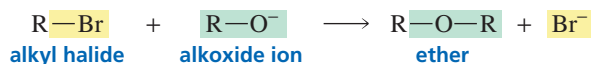
PROBLEM 29♦

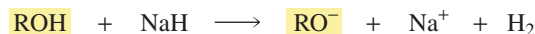
a. In which solvent would *tert*-butyl bromide undergo an S_N1 reaction more rapidly: 50% water and 50% ethanol or 100% ethanol?
b. How would the products differ in the two solvents?

8.13 SUBSTITUTION REACTIONS IN SYNTHESIS

In Section 8.2, you saw that nucleophilic substitution reactions of alkyl halides can lead to a wide variety of organic compounds. For example, ethers are synthesized by the reaction of an alkyl halide with an alkoxide ion. This reaction, called the Williamson ether synthesis (after Alexander Williamson, who discovered it in 1850) is still considered one of the best ways to synthesize an ether.

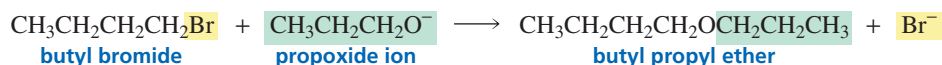
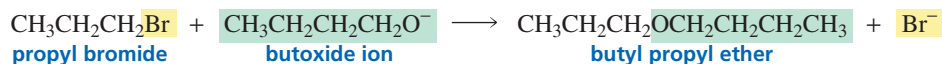
Williamson ether synthesis

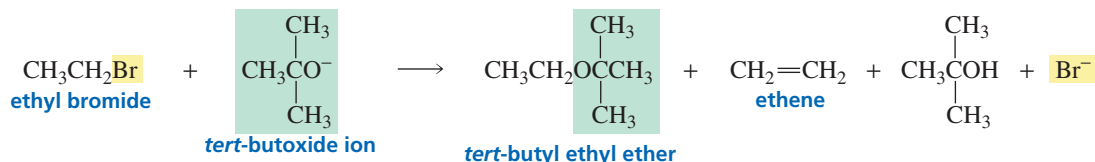
$$\underset{\text{alkyl halide}}{R{-}Br} + \underset{\text{alkoxide ion}}{R{-}O^-} \longrightarrow \underset{\text{ether}}{R{-}O{-}R} + Br^-$$

The alkoxide ion (RO^-) for a **Williamson ether synthesis** can be prepared by using sodium hydride (NaH) to remove a proton from an alcohol.

$$ROH + NaH \longrightarrow RO^- + Na^+ + H_2$$

The Williamson ether synthesis is a nucleophilic substitution reaction. It requires a high concentration of a good nucleophile, which indicates that it is an S_N2 reaction.

If you want to synthesize an ether such as the one shown next, you have a choice of starting materials: you can use either a propyl halide and butoxide ion or a butyl halide and propoxide ion.

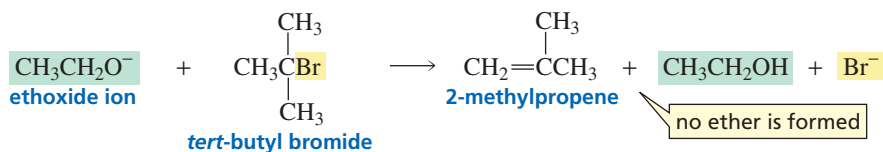
$$\underset{\text{propyl bromide}}{CH_3CH_2CH_2Br} + \underset{\text{butoxide ion}}{CH_3CH_2CH_2CH_2O^-} \longrightarrow \underset{\text{butyl propyl ether}}{CH_3CH_2CH_2OCH_2CH_2CH_2CH_3} + Br^-$$

$$\underset{\text{butyl bromide}}{CH_3CH_2CH_2CH_2Br} + \underset{\text{propoxide ion}}{CH_3CH_2CH_2O^-} \longrightarrow \underset{\text{butyl propyl ether}}{CH_3CH_2CH_2CH_2OCH_2CH_2CH_3} + Br^-$$

However, if you want to synthesize *tert*-butyl ethyl ether, the starting materials must be an ethyl halide and *tert*-butoxide ion.

$$\underset{\text{ethyl bromide}}{CH_3CH_2Br} + \underset{\textit{tert}\text{-butoxide ion}}{(CH_3)_3CO^-} \longrightarrow \underset{\textit{tert}\text{-butyl ethyl ether}}{CH_3CH_2OC(CH_3)_3} + \underset{\text{ethene}}{CH_2{=}CH_2} + (CH_3)_3COH + Br^-$$

If, instead, you used a *tert*-butyl halide and ethoxide ion, you would not obtain any ether because the reaction of a tertiary alkyl halide under S_N2/E2 conditions forms only the elimination product.

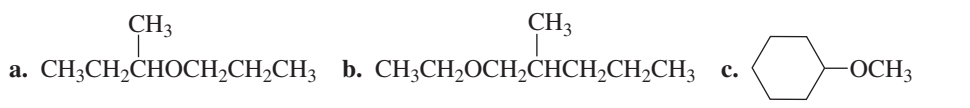
In ether synthesis, the less hindered group should be provided by the alkyl halide.

$$\underset{\text{ethoxide ion}}{CH_3CH_2O^-} + \underset{\textit{tert}\text{-butyl bromide}}{(CH_3)_3CBr} \longrightarrow \underset{\text{2-methylpropene}}{CH_2{=}C(CH_3)CH_3} + CH_3CH_2OH + Br^-$$

no ether is formed

Consequently, a Williamson ether synthesis should be designed in such a way that the *less hindered alkyl group* is provided by the *alkyl halide* and the *more hindered alkyl group* comes from the *alkoxide ion*.

PROBLEM 30

What would be the best way to prepare the following ethers using an alkyl halide and an alcohol?

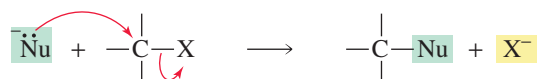
a. $CH_3CH_2CH(CH_3)OCH_2CH_2CH_3$ **b.** $CH_3CH_2OCH_2CH(CH_3)CH_2CH_2CH_3$ **c.** cyclohexyl–OCH_3

SOME IMPORTANT THINGS TO REMEMBER

- Alkyl halides undergo two kinds of **nucleophilic substitution reactions:** S_N2 and S_N1. In both reactions, a nucleophile substitutes for a halogen.
- An **S_N2 reaction** is **bimolecular:** both the alkyl halide and the nucleophile are involved in the transition state of the rate-limiting step, so the rate of the reaction depends on the concentration of both of them.
- An S_N2 reaction has a one-step mechanism: the nucleophile attacks the back side of the carbon that is attached to the halogen.
- The rate of an S_N2 reaction decreases as the size of the groups at the back side of the carbon undergoing attack increases. Therefore, the relative reactivities of alkyl halides in an S_N2 reaction are: $1° > 2° > 3°$.
- An S_N2 reaction takes place with **inversion of configuration.**
- An S_N1 reaction is **unimolecular;** only the alkyl halide is involved in the transition state of the rate-limiting step, so the rate of the reaction is dependent only on the concentration of the alkyl halide.
- An S_N1 reaction has a two-step mechanism: the halogen departs in the first step, forming a carbocation intermediate that is attacked by a nucleophile in the second step. Most S_N1 reactions are **solvolysis** reactions, meaning the solvent is the nucleophile.
- The rate of an S_N1 reaction depends on the ease of carbocation formation and the nature of the leaving group.
- An S_N1 reaction takes place with both inversion and retention of configuration.
- Primary alkyl halides, secondary alkyl halides, and methyl halides undergo only S_N2 reactions.
- Tertiary alkyl halides undergo only S_N1 reactions.
- The relative reactivities of alkyl halides that differ only in the halogen atom are: $RI > RBr > RCl > RF$ in *both* S_N2, S_N1, E2, and E1 reactions.
- **Basicity** is a measure of how well a compound shares its lone pair with a proton; **nucleophilicity** is a measure of how readily a species with a lone pair is able to attack an electron-deficient atom.
- In general, a stronger base is a better nucleophile.
- If the two functional groups of a **bifunctional molecule** can react with each other, both **intermolecular** (between two molecules) and **intramolecular** (within one molecule) **reactions** can occur. The reaction that is more likely to occur depends on the concentration of the bifunctional molecule and the size of the ring that would be formed in the intramolecular reaction.
- In addition to undergoing nucleophilic substitution reactions, alkyl halides undergo elimination reactions. The product of an **elimination reaction** is an alkene.
- An **E2 reaction** is a one-step reaction in which the proton and the halide ion are removed in the same step.
- An **E1 reaction** is a two-step reaction in which the alkyl halide dissociates, forming a carbocation intermediate. Then, a base removes a proton from a carbon adjacent to the positively charged carbon.
- Primary and secondary alkyl halides undergo only E2 reactions. Tertiary alkyl halides undergo both E2 and E1 reactions.
- The relative reactivities of alkyl halides in an E2 reaction are: $3° > 2° > 1°$.
- S_N2 and E2 reactions are favored by a high concentration of a strong nucleophile/base and S_N1 and E1 reactions are favored by a weak nucleophile/base.
- E2 and E1 reactions are regioselective; the major product is the more stable alkene.
- The more stable alkene is formed when a hydrogen is removed from the β-carbon bonded to the fewest hydrogens.
- E2 and E1 reactions are regioselective: the major product is the more stable alkene.
- E2 and E1 reactions are also stereoselective: the major product is the alkene with the largest groups on opposite sides of the double bond.
- When S_N2/E2 reactions are favored, primary alkyl halides form primarily substitution products. Secondary alkyl halides form both substitution and elimination products. Tertiary alkyl halides form only elimination products.

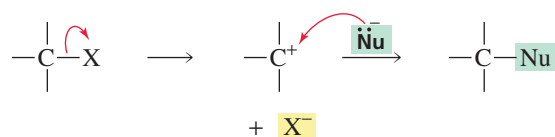
- When S_N1/E1 conditions are favored, tertiary alkyl halides form both substitution and elimination products; primary and secondary alkyl halides do not undergo S_N1/E1 solvolysis reactions.
- Increasing the polarity of the solvent will decrease the rate of the reaction if one or more reactants that participate in the rate-determining step are charged, and it will increase the rate of the reaction if none of the reactants that participate in the rate-determining step is charged.
- The **Williamson ether synthesis** prepares ethers from the reaction of an alkyl halide with an alkoxide ion.

SUMMARY OF REACTIONS

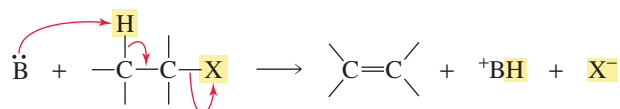
1. An S_N2 reaction has a one-step mechanism:

$$\ddot{Nu}^- + -\overset{|}{\underset{|}{C}}-X \longrightarrow -\overset{|}{\underset{|}{C}}-Nu + X^-$$

Relative reactivities: $CH_3X > 1° > 2° > 3°$. Tertiary alkyl halides cannot undergo S_N2 reactions.
Only the inverted product is formed.

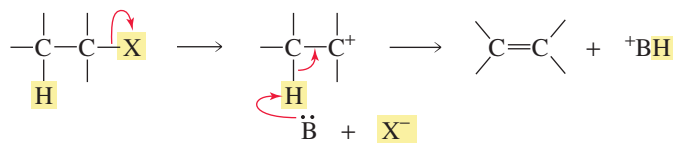
2. An S_N1 reaction has a two-step mechanism with a carbocation intermediate.

$$-\overset{|}{\underset{|}{C}}-X \longrightarrow -\overset{|}{\underset{|}{C^+}} + X^- \xrightarrow{\ddot{Nu}^-} -\overset{|}{\underset{|}{C}}-Nu$$

Reactivity: only tertiary alkyl halides undergo S_N1 solvolysis reactions.
Products with both inverted and retained configurations are formed.

3. An E2 reaction has a one-step mechanism; the major product is obtained by removing a hydrogen from the β-carbon bonded to the fewest hydrogens.

$$\ddot{B} + -\overset{H}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-X \longrightarrow \rangle C{=}C\langle + {}^+BH + X^-$$

Relative reactivities of alkyl halides: $3° > 2° > 1°$
The more stable alkene is the major product. If it has *E* and *Z* stereoisomers, the stereoisomer with the largest groups on opposite sides of the double bond is the major product.

4. An E1 reaction has a two-step mechanism with a carbocation intermediate; the major product is obtained by removing a hydrogen from the β-carbon bonded to the fewest hydrogens.

$$-\underset{H}{\overset{|}{C}}-\overset{|}{\underset{|}{C}}-X \longrightarrow -\underset{H}{\overset{|}{C}}-\overset{|}{\underset{|}{C^+}} + X^- \xrightarrow{\ddot{B}} \rangle C{=}C\langle + {}^+BH$$

Only tertiary alkyl halides undergo E1 reactions.
The more stable alkene is the major product. If it has *E* and *Z* stereoisomers, the stereoisomer with the largest groups on opposite sides of the double bond is the major product.

PROBLEMS

31. Which reaction in each of the following pairs will take place more rapidly?

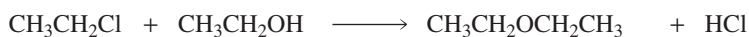
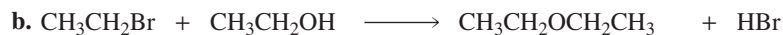
a. $CH_3CH_2Cl + CH_3CH_2OH \longrightarrow CH_3CH_2OCH_2CH_3 + HCl$

$CH_3CH_2Cl + CH_3CH_2O^- \longrightarrow CH_3CH_2OCH_2CH_3 + Cl^-$

b. $CH_3CH_2Br + CH_3CH_2OH \longrightarrow CH_3CH_2OCH_2CH_3 + HBr$

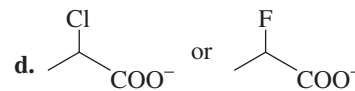
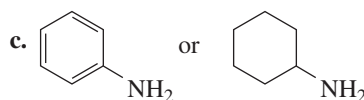
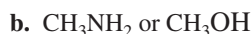
$CH_3CH_2Cl + CH_3CH_2OH \longrightarrow CH_3CH_2OCH_2CH_3 + HCl$

c. $CH_3CH_2I + CH_3CH_2NH_2 \longrightarrow CH_3CH_2\overset{+}{N}H_2CH_2CH_3 + I^-$

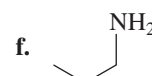
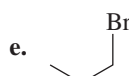
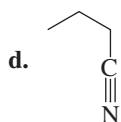
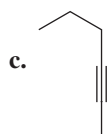
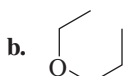
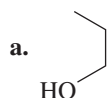
$CH_3CH_2I + CH_3CH_2OH \longrightarrow CH_3CH_2OCH_2CH_3 + HI$

32. Give the product of the reaction of ethyl chloride with each of the following nucleophiles:

a. HO^- **b.** $^-NHCH_3$ **c.** H_2O **d.** CH_3S^- **e.** CH_3O^- **f.** $CH_3CH_2CH_2NH_2$

33. Which is a better nucleophile?

a. H_2S or HS^- **b.** CH_3NH_2 or CH_3OH **c.** (aniline, NH_2) or (cyclohexylamine, NH_2) **d.** (Cl, COO^-) or (F, COO^-)

34. For each of the pairs in Problem 33, indicate which is a better leaving group.

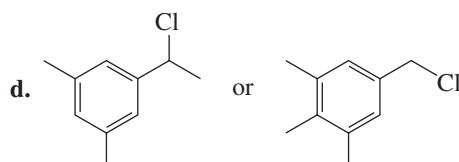
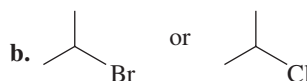
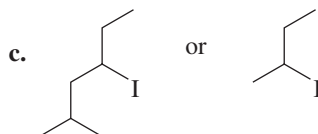
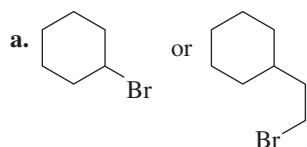
35. What nucleophiles could be used to react with propyl iodide to prepare the following compounds?

a. HO **b.** O **c.** **d.** C≡N **e.** Br **f.** NH_2

36. Which alkyl halide in each pair would you expect to be more reactive in an S_N2 reaction with a given nucleophile?

a. Br or Br

b. Br or Cl

c. I or I

d. Cl or Cl

37. Explain how the following changes would affect the rate of the substitution reaction of 1-bromobutane with methoxide ion in DMF.

a. The concentration of both the alkyl halide and the nucleophile are tripled.

b. The solvent is changed to ethanol.

c. The nucleophile is changed to ethanol.

d. The alkyl halide is changed to 1-chlorobutane.

e. The alkyl halide is changed to 2-bromobutane.

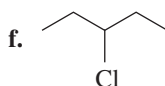
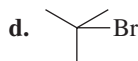
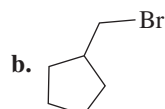
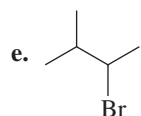
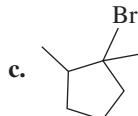
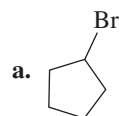
38. Explain how the following changes would affect the rate of the substitution reaction of 2-bromo-2-methylbutane with methanol:

a. The alkyl halide is changed to 2-chloro-2-methylbutane.

b. The nucleophile is changed to ethanol.

39. Draw the major product obtained when each of the following alkyl halides undergoes an E2 reaction:

a. Br **c.** Br **e.** Br

b. Br **d.** Br **f.** Cl

40. Which alkyl halide in Problem 39 can undergo an E1 reaction? What would be the major product?

41. For each of the following reactions, give the substitution products; if the products can exist as stereoisomers, show what stereoisomers are obtained:

a. (*R*)-2-bromopentane + high concentration of CH_3O^-
b. *trans*-1-bromo-4-methylcyclohexane + high concentration of CH_3O^-
c. 3-bromo-3-methylpentane + CH_3OH
d. (*R*)-3-bromo-3-methylhexane + CH_3OH
e. 1-bromo-1-methylcyclohexane + CH_3OH

42. Starting with an alkyl halide, how could the following compounds be prepared?

a. 2-methoxybutane **b.** 1-methoxybutane **c.** dicyclohexyl ether

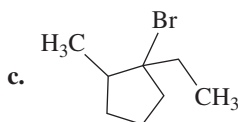
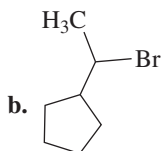
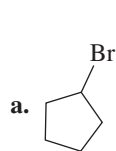
43. Which reactant in each of the following pairs will undergo an elimination reaction more rapidly?

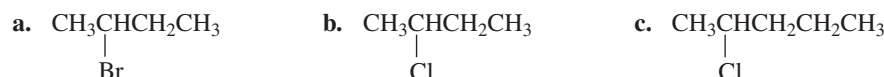
a. $(CH_3)_3CCl \xrightarrow[H_2O]{HO^-}$ or $(CH_3)_3CI \xrightarrow[H_2O]{HO^-}$ **b.** $(CH_3)_3CBr \xrightarrow[H_2O]{HO^-}$ or $(CH_3)_2CHBr \xrightarrow[H_2O]{HO^-}$

44. Give the major product obtained when each of the following alkyl halides undergoes an E2 reaction:

a.

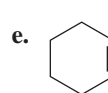
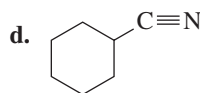
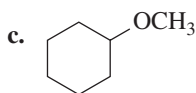
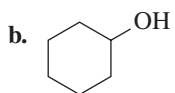
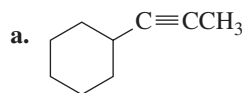
b.

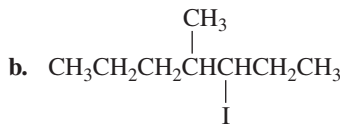
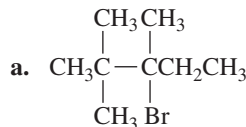
c.

45. What stereoisomer would be obtained in greater yield when each of the following alkyl halides undergoes an E2 reaction:

a. $CH_3CH(Br)CH_2CH_3$ **b.** $CH_3CH(Cl)CH_2CH_3$ **c.** $CH_3CH(Cl)CH_2CH_2CH_3$

46. For each of the following reactions, give the major elimination product; if the product can exist as stereoisomers, indicate which stereoisomer is obtained in greater yield:

a. (*R*)-2-bromohexane + high concentration of HO^-
b. (*R*)-3-bromo-2,3-dimethylpentane + high concentration of HO^-
c. 3-bromo-3-methylpentane + high concentration of HO^-
d. 3-bromo-3-methylpentane + H_2O

47. Starting with bromocyclohexane, how could the following compounds be prepared?

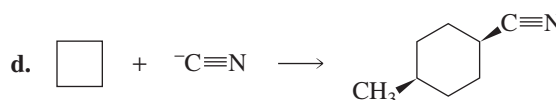
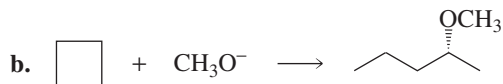
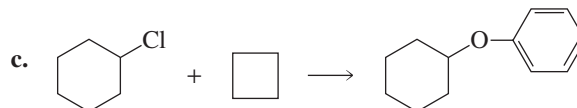
a. cyclohexyl–C≡CCH$_3$ **b.** cyclohexyl–OH **c.** cyclohexyl–OCH$_3$ **d.** cyclohexyl–C≡N **e.** cyclohexene

48. Which stereoisomer would be obtained in greater yield from an E2 reaction of each of the following alkyl halides?

a. $CH_3C(CH_3)_2-C(CH_3)(Br)CH_2CH_3$ **b.** $CH_3CH_2CH_2CH(CH_3)CH(I)CH_2CH_3$

49. Fill in the blanks in the following chemical equations:

a. (butyl)Br + ☐ ⟶ (butyl)OCH$_3$

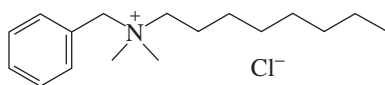
b. ☐ + CH_3O^- ⟶ (2-methoxybutane, OCH$_3$ hashed)

c. (cyclohexyl)Cl + ☐ ⟶ (cyclohexyl)–O–(phenyl)

d. ☐ + $^-C{\equiv}N$ ⟶ (cyclohexane with wedged C≡N and wedged CH$_3$)

50. For each of the following alkyl halides, indicate what stereoisomer would be obtained in greatest yield if it reacts with a high concentration of ethoxide ion.

a. 3-bromo-2,2,3-trimethylpentane
b. 4-bromo-2,2,3,3-tetramethylpentane
c. 3-bromo-2,3-dimethylpentane
d. 3-bromo-3,4-dimethylhexane

51. Alkylbenzyldimethyl ammonium chloride is a leave-on skin antiseptic used to treat such things as cuts and cold sores. It is also the antiseptic in many hand sanitizers. It is actually a mixture of compounds that differ in the number of carbons (any even number between 8 and 18) in the alkyl group. Show three different sets of reagents (each set composed of an alkyl chloride and an amine) that can be used to synthesize the alkylbenzyldimethyl ammonium chloride shown here.

(benzyl)–$\overset{+}{N}(CH_3)_2$–(octyl) Cl^-

52. **a.** Explain why 1-bromo-2,2-dimethylpropane has difficulty undergoing either S_N2 or S_N1 reactions.
b. Can it undergo E2 and E1 reactions?

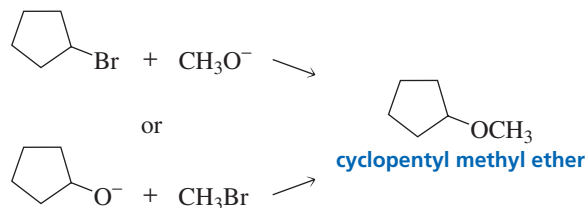
53. An ether can be prepared by an S_N2 reaction of an alkyl halide with an alkoxide ion (RO^-). Which set of alkyl halide and alkoxide ion would give you a better yield of cyclopentyl methyl ether?

Br + CH_3O^- →

or

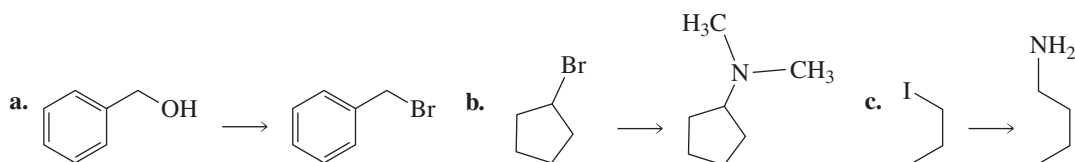
O$^-$ + CH_3Br →

OCH_3

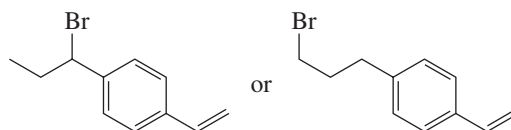
cyclopentyl methyl ether

54. Give two sets of reactants (each set including an alkyl halide and a nucleophile) that could be used to synthesize the following ether:

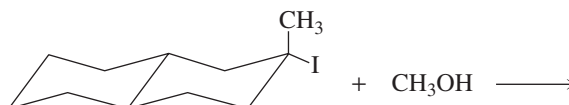
$CH_3CH_2OCH_2CH_2CHCH_3$ (with CH_3 on the CH)

55. Show how the following compounds could be synthesized using the given starting materials:

a. OH → Br **b.** Br → H_3C—N—CH_3 **c.** I → NH_2

56. Indicate which of the compounds will give a higher substitution-product to elimination-product ratio when it reacts with isopropyl bromide: ethoxide ion or *tert*-butoxide ion.

57. Which alkyl halide undergoes an E1 reaction more rapidly?

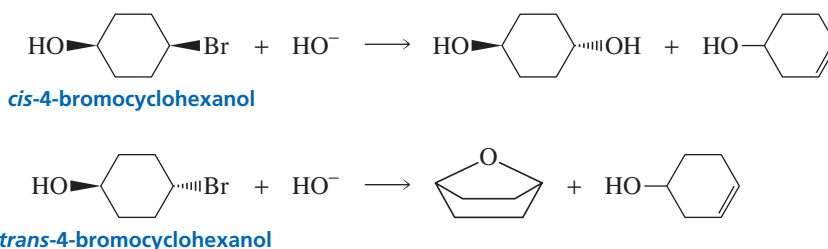
Br or Br

58. Draw the structures of the products obtained from the following reaction:

CH_3 I + CH_3OH ⟶

59. *cis*-4-Bromocyclohexanol and *trans*-4-bromocyclohexanol form the same elimination product but a different substitution product when they react with HO^-.

HO—Br + HO^- ⟶ HO—OH + HO—

cis-4-bromocyclohexanol

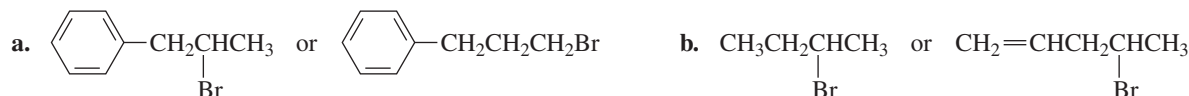
HO—Br + HO^- ⟶ O + HO—

trans-4-bromocyclohexanol

a. Why do they form the same elimination product?
b. Explain, by showing the mechanisms, why different substitution products are obtained.
c. How many stereoisomers does each of the elimination and substitution reactions form?

60. A cyclic compound can be formed by an intramolecular reaction. Draw the structure of the ether that would be formed from each of the following intramolecular reactions.

a. $BrCH_2CH_2CH_2CH_2O^-$ ⟶ ether **b.** $ClCH_2CH_2CH_2CH_2CH_2O^-$ ⟶ ether

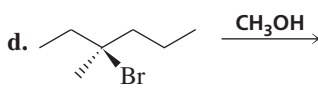
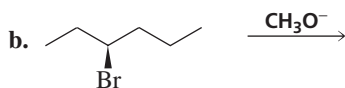
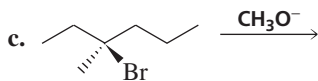
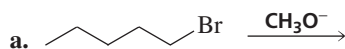
61. Which of the following is more reactive in an E2 reaction?

a. C_6H_5—CH_2CHCH_3 (Br on CH) or C_6H_5—$CH_2CH_2CH_2Br$ **b.** $CH_3CH_2CHCH_3$ (Br on CH) or $CH_2{=}CHCH_2CHCH_3$ (Br on CH)

62. Draw the elimination products obtained under E2 conditions for each of the following alkyl halides, indicating major and minor products.

a. Br $\xrightarrow{CH_3O^-}$

b. Br $\xrightarrow{CH_3O^-}$

c. Br $\xrightarrow{CH_3O^-}$

d. Br $\xrightarrow{CH_3OH}$

63. a. Identify the substitution products that form when 2-bromo-2-methylpropane is dissolved in a mixture of 80% ethanol and 20% water.

b. Explain why the same products are obtained when 2-chloro-2-methylpropane is dissolved in a mixture of 80% ethanol and 20% water.

64. The rate of the reaction of methyl iodide with quinuclidine was measured and then the rate of the reaction of methyl iodide with triethylamine was measured in the same solvent. The concentration of the reagents was the same in both experiments.

a. Which reaction was faster?

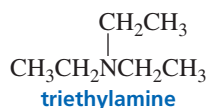
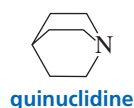
b. Which reaction had the larger rate constant?

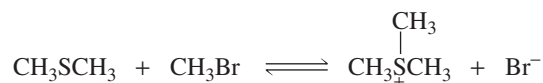
N

quinuclidine

CH_2CH_3

$CH_3CH_2NCH_2CH_3$

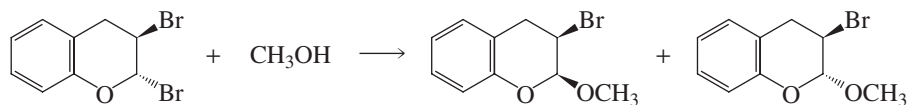
triethylamine

65. In which solvent—ethanol or diethyl ether—would the equilibrium for the following S_N2 reaction lie farther to the right?

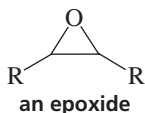
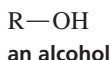
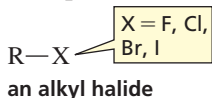
$$CH_3SCH_3 + CH_3Br \rightleftharpoons CH_3\overset{CH_3}{\overset{|}{\underset{+}{S}}}CH_3 + Br^-$$

66. The pK_a of acetic acid in water is 4.76. What effect would a decrease in the polarity of the solvent have on the pK_a? Why?

67. a. Propose a mechanism for the following reaction?

b. Explain why two products are formed.

c. Explain why methanol substitutes for only one of the bromines.

Br, O, Br + CH_3OH ⟶ Br, O, OCH_3 + Br, O, OCH_3

9 Reactions of Alcohols, Ethers, Epoxides, Amines, and Thiols

dried coca leaves

Chemists search the world for plants and berries and search the ocean for flora and fauna that might be used as the source of a lead compound for the development of a new drug. In this chapter, we will see how cocaine, which is obtained from the leaves of Erythroxylon coca*—a bush native to the highlands of the South American Andes, was used as the source of a lead compound for the development of some common anesthetics.*

We have seen that alkyl halides, a family of compounds in Group III, undergo substitution and/or elimination reactions because of their electron-withdrawing halogen atoms (Chapter 8). Other families of compounds in Group III also have electron-withdrawing groups, and they too undergo substitution and/or elimination reactions. The relative reactivity of these compounds depends on the electron-withdrawing group—that is, on the leaving group.

The leaving groups of alcohols and ethers (HO^-, RO^-) are much stronger bases than the leaving group of an alkyl halide. Because they are stronger bases, they are poorer leaving groups and, therefore, are harder to displace. Consequently, alcohols and ethers are less reactive than alkyl halides in substitution and elimination reactions. In this Chapter we will see that alcohols and ethers have to be "activated" before they can undergo a substitution or an elimination reaction.

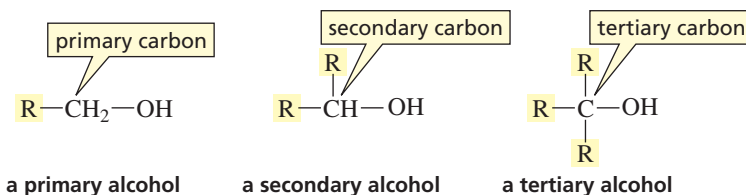
9.1 THE NOMENCLATURE OF ALCOHOLS

Before we look at the reactions of alcohols, we need to learn how to name them. Recall that an **alcohol** is a compound in which a hydrogen of an alkane has been replaced by an OH group (Section 3.1). We have seen that alcohols are classified as

primary, **secondary**, or **tertiary**, depending on whether the OH group is bonded to a primary, secondary, or tertiary carbon—the same way alkyl halides are classified (Section 3.5).

primary carbon: $R-CH_2-OH$ — **a primary alcohol**

secondary carbon: $R-CH(R)-OH$ — **a secondary alcohol**

tertiary carbon: $R-C(R)(R)-OH$ — **a tertiary alcohol**

The common name of an alcohol consists of the name of the alkyl group to which the OH group is attached, followed by the word "alcohol."

CH_3CH_2OH — **ethyl alcohol**

$CH_3CH_2CH_2OH$ — **propyl alcohol**

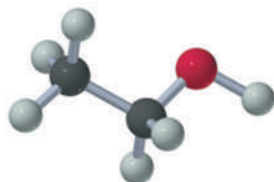
$CH_3CH(CH_3)OH$ — **isopropyl alcohol**

methyl alcohol

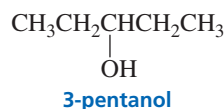
ethyl alcohol

propyl alcohol

The IUPAC system uses the suffix "ol" to denote the OH group. Thus, the systematic name of an alcohol is obtained by replacing the "e" at the end of the name of the parent hydrocarbon with the suffix "ol." This should remind you of the suffix "ene" used to denote the functional group of an alkene (Section 5.1).

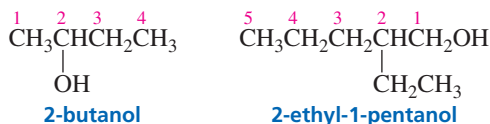
CH_3OH — **methanol**

CH_3CH_2OH — **ethanol**

When necessary, the position of the functional group is indicated by a number.

$CH_3CH_2CH(OH)CH_2CH_3$ — **3-pentanol**

Let's review the rules used to name a compound that has a functional group suffix:

1. The parent hydrocarbon is the longest chain containing the functional group. The parent chain is numbered in the direction that gives the *functional group suffix the lowest possible number*.

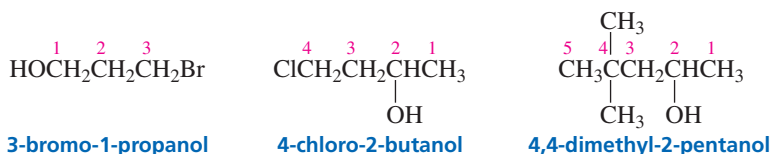
$\overset{1}{C}H_3\overset{2}{C}H(OH)\overset{3}{C}H_2\overset{4}{C}H_3$ — **2-butanol**

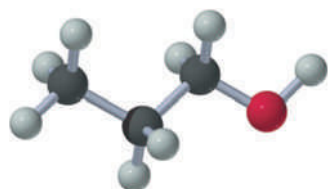
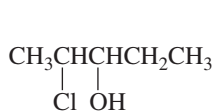
$\overset{5}{C}H_3\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}H(CH_2CH_3)\overset{1}{C}H_2OH$ — **2-ethyl-1-pentanol**

The longest continuous chain has six carbons, but the longest continuous chain containing the OH functional group has five carbons so the compound is named as a pentanol.

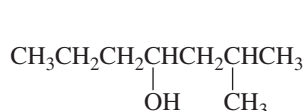
2. If there is a functional group suffix and a substituent, the functional group suffix gets the lowest possible number.

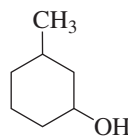
$HO\overset{1}{C}H_2\overset{2}{C}H_2\overset{3}{C}H_2Br$ — **3-bromo-1-propanol**

$Cl\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}H(OH)\overset{1}{C}H_3$ — **4-chloro-2-butanol**

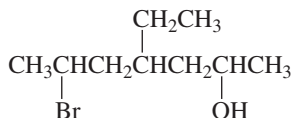
$\overset{5}{C}H_3\overset{4}{C}(CH_3)_2\overset{3}{C}H_2\overset{2}{C}H(OH)\overset{1}{C}H_3$ — **4,4-dimethyl-2-pentanol**

3. If counting in either direction gives the same number for the functional group suffix, then the chain is numbered in the direction that gives a substituent the lowest possible number. Notice that a number is not needed to designate the position of a functional group suffix in a cyclic compound, because it is assumed to be at the 1-position.

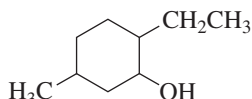
$CH_3CHCHCH_2CH_3$ (Cl on C2, OH on C3)

2-chloro-3-pentanol
not
4-chloro-3-pentanol

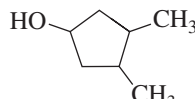
$CH_3CH_2CH_2CHCH_2CHCH_3$ (OH on C4, CH_3 on C6)

2-methyl-4-heptanol
not
6-methyl-4-heptanol

(cyclohexane ring with CH_3 and OH)

3-methylcyclohexanol
not
5-methylcyclohexanol

4. If there is more than one substituent, the substituents are stated in alphabetical order.

$CH_3CHCH_2CHCH_2CHCH_3$ (Br on C2, CH_2CH_3 on C4, OH on C6)

6-bromo-4-ethyl-2-heptanol

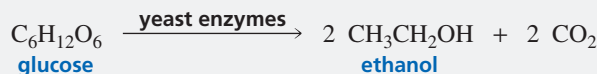
(cyclohexane ring with CH_2CH_3, OH, and H_3C)

2-ethyl-5-methylcyclohexanol

(cyclopentane ring with HO, CH_3, and CH_3)

3,4-dimethylcyclopentanol

Grain Alcohol and Wood Alcohol

When ethanol is ingested, it acts on the central nervous system. Moderate amounts affect judgment and lower inhibitions. Higher amounts interfere with motor coordination and cause slurred speech and amnesia. Still higher amounts cause nausea and loss of consciousness. Ingesting very large amounts of ethanol interferes with spontaneous respiration and can be fatal.

The ethanol in alcoholic beverages is produced by the fermentation of glucose, generally obtained from grapes or from grains such as corn, rye, and wheat (which is why ethanol is also known as grain alcohol). Grains are cooked in the presence of malt (sprouted barley) to convert much of their starch into glucose. Yeast enzymes are added to convert the glucose into ethanol and carbon dioxide (Section 19.5).

$$\underset{\text{glucose}}{C_6H_{12}O_6} \xrightarrow{\text{yeast enzymes}} 2\ \underset{\text{ethanol}}{CH_3CH_2OH} + 2\ CO_2$$

The kind of beverage produced (white or red wine, beer, scotch, bourbon, champagne) depends on the plant species providing the glucose, whether the CO_2 formed in the fermentation is allowed to escape, whether other substances are added, and how the beverage is purified (by sedimentation, for wines; by distillation, for scotch and bourbon).

The tax imposed on liquor would make ethanol a prohibitively expensive laboratory reagent. Laboratory alcohol, therefore, is not taxed because ethanol is needed in a wide variety of commercial processes. Although not taxed, it is carefully regulated by the federal government to make certain that it is not used for the preparation of alcoholic beverages. Denatured alcohol—ethanol that has been made undrinkable by the addition of a denaturant such as benzene or methanol—is not taxed, but the added impurities make it unfit for many laboratory uses.

Methanol, also known as wood alcohol (because at one time it was obtained by heating wood in the absence of oxygen), is highly toxic. Ingesting even very small amounts can cause blindness, and ingesting as little as an ounce has been fatal.

PROBLEM 1

Draw the structures of straight-chain alcohols that have from one to six carbons with an OH group at the end of the chain, and then give each of them a common name and a systematic name.

PROBLEM 2♦

Give each of the following a systematic name, and indicate whether each is a primary, secondary, or tertiary alcohol:

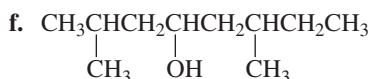
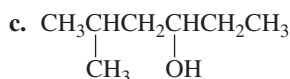
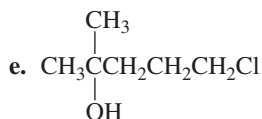
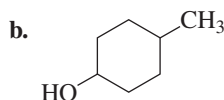
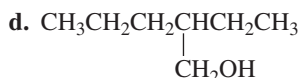
a. $CH_3CH_2CH_2CH_2CH_2OH$

b. (cyclohexane ring with CH_3 and HO)

c. $CH_3CHCH_2CHCH_2CH_3$ (CH_3 on C2, OH on C4)

d. $CH_3CH_2CH_2CHCH_2CH_3$ (CH_2OH on C4)

e. $CH_3CCH_2CH_2CH_2Cl$ (CH_3 and OH on C2)

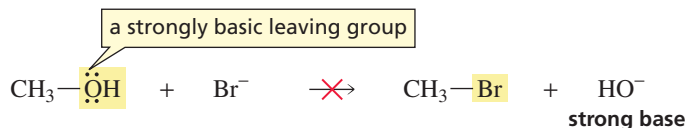
f. $CH_3CHCH_2CHCH_2CHCH_2CH_3$ (CH_3 on C2, OH on C4, CH_3 on C6)

PROBLEM 3♦

Write the structures of all the tertiary alcohols with molecular formula $C_6H_{14}O$, and give each a systematic name.

9.2 ACTIVATING AN ALCOHOL FOR NUCLEOPHILIC SUBSTITUTION BY PROTONATION

An **alcohol** has a strongly basic leaving group (HO^-) that cannot be displaced by a nucleophile. Therefore, an alcohol cannot undergo a nucleophilic substitution reaction.

$$CH_3{-}\ddot{O}H + Br^- \not\rightarrow CH_3{-}Br + HO^-$$

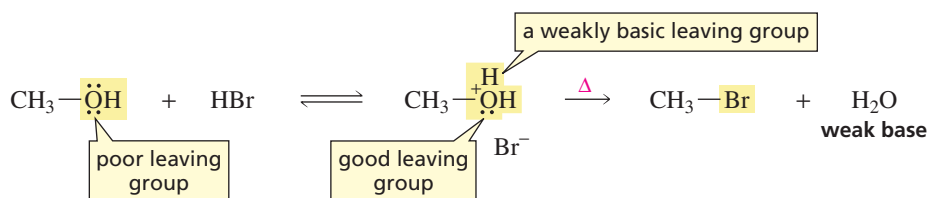
a strongly basic leaving group (OH); strong base (HO^-)

However, if the alcohol's OH group is converted into a group that is a weaker base (and therefore a better leaving group), a nucleophilic substitution reaction can occur.

The stronger the acid, the weaker its conjugate base.

When bases with similar features are compared, it is found that the weaker the base, the more easily it can be displaced.

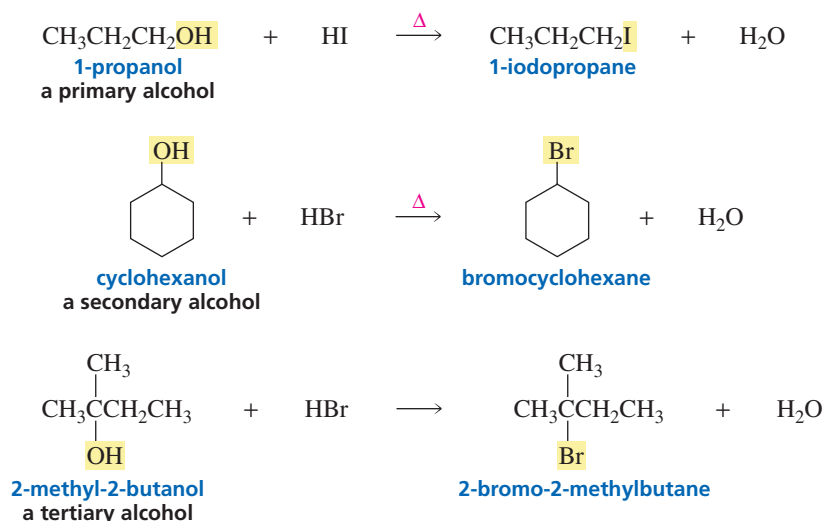
One way to convert an OH group into a weaker base is to protonate it by adding acid to the reaction mixture. Protonation changes the leaving group from HO^- to H_2O, which is a weak enough base to be displaced by a nucleophile. The substitution reaction is slow and requires heat (except in the case of tertiary alcohols) if it is to take place at a reasonable rate.

$$CH_3{-}\ddot{O}H + HBr \rightleftharpoons CH_3{-}\overset{+}{O}H_2 \;\; Br^- \xrightarrow{\Delta} CH_3{-}Br + H_2O$$

poor leaving group (OH); good leaving group / a weakly basic leaving group ($\overset{+}{O}H_2$); weak base (H_2O)

Because the OH group of the alcohol has to be protonated before it can be displaced by a nucleophile, only weakly basic nucleophiles (I^-, Br^-, Cl^-) can be used in the substitution reaction. Moderately and strongly basic nucleophiles (NH_3, RNH_2, and CH_3O^-) cannot be used because they too would be protonated in the acidic solution and, once protonated, would no longer be nucleophiles ($^+NH_4$, $R\overset{+}{N}H_3$) or would be poor nucleophiles (CH_3OH).

PROBLEM 4♦

Why are NH_3 and CH_3NH_2 no longer nucleophiles when they are protonated?

Primary, secondary, and tertiary alcohols all undergo nucleophilic substitution reactions with HI, HBr, and HCl to form alkyl halides. Only the tertiary alcohol has to be heated.

$$CH_3CH_2CH_2OH + HI \xrightarrow{\Delta} CH_3CH_2CH_2I + H_2O$$

1-propanol (a primary alcohol) → 1-iodopropane

$$\text{cyclohexanol} + HBr \xrightarrow{\Delta} \text{bromocyclohexane} + H_2O$$

cyclohexanol (a secondary alcohol) → bromocyclohexane

$$CH_3C(CH_3)(OH)CH_2CH_3 + HBr \longrightarrow CH_3C(CH_3)(Br)CH_2CH_3 + H_2O$$

2-methyl-2-butanol (a tertiary alcohol) → 2-bromo-2-methylbutane

The mechanism of the substitution reaction depends on the structure of the alcohol. Secondary and tertiary alcohols undergo S_N1 reactions.

MECHANISM FOR THE S_N1 REACTION OF AN ALCOHOL

$$(CH_3)_3C{-}\ddot{O}H + H{-}Br \rightleftharpoons (CH_3)_3C{-}\overset{+}{O}H_2 \rightleftharpoons (CH_3)_3C^+ + H_2O \xrightarrow{:\ddot{Br}:^-} (CH_3)_3C{-}Br$$

$$(CH_3)_3C^+ \rightleftharpoons CH_3C(CH_3){=}CH_2 + H^+ \xrightarrow{HBr} (CH_3)_3C{-}Br$$

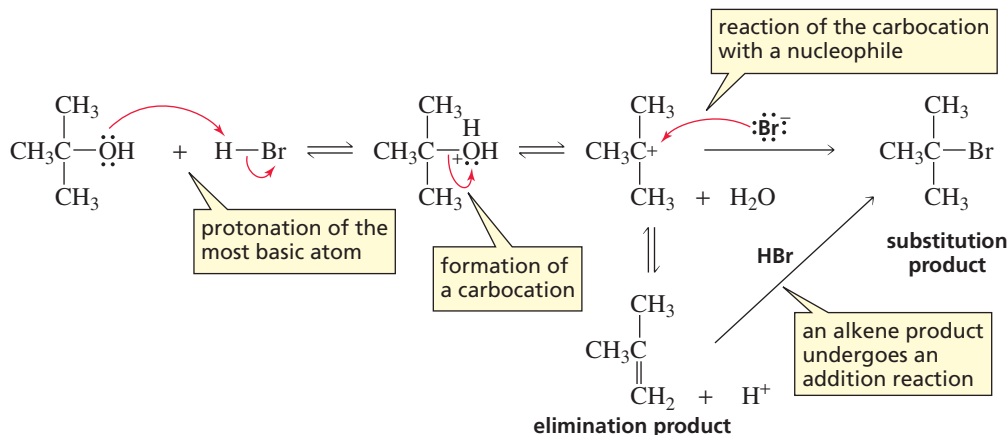
protonation of the most basic atom

formation of a carbocation

reaction of the carbocation with a nucleophile

substitution product

elimination product

an alkene product undergoes an addition reaction

An acid protonates the most basic atom in a molecule.

- An acid always reacts with an organic molecule in the same way: it protonates the most basic atom in the molecule.
- Weakly basic water is the leaving group that is expelled, forming a carbocation.
- The carbocation, like the carbocation formed when an alkyl halide dissociates in an S_N1 reaction, has two possible fates: it can combine with a nucleophile and form a substitution product, or it can lose a proton and form an elimination product (Section 8.11).

Although the reaction can form both a substitution product and an elimination product, little elimination product is actually obtained because the alkene formed in an elimination reaction can undergo a subsequent electrophilic addition reaction with HBr to form more of the substitution product (Section 6.1).

Tertiary alcohols undergo substitution reactions with hydrogen halides faster than secondary alcohols do, because tertiary carbocations are more stable and, therefore, are formed more rapidly than secondary carbocations. (Recall that alkyl groups stabilize carbocations by hyperconjugation; Section 6.2.) As a result, the reaction of a tertiary alcohol with a hydrogen halide proceeds readily at room temperature, whereas the reaction of a secondary alcohol with a hydrogen halide has to be heated to have the reaction occur at a reasonable rate.

Primary alcohols cannot undergo S_N1 reactions because primary carbocations are too unstable to be formed, even when the reaction is heated (Section 8.3). Therefore, when a primary alcohol reacts with a hydrogen halide, it must do so by an S_N2 reaction.

Carbocation stability: 3° > 2° > 1°

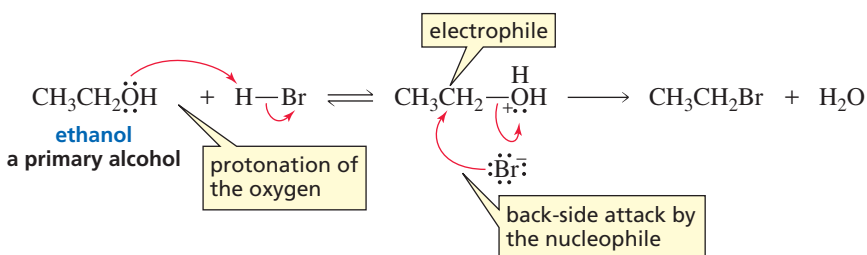
MECHANISM FOR THE S_N2 REACTION OF AN ALCOHOL

$$CH_3CH_2\ddot{O}H + H{-}Br \rightleftharpoons CH_3CH_2{-}\overset{+}{O}H_2 + :\ddot{Br}:^- \longrightarrow CH_3CH_2Br + H_2O$$

ethanol
a primary alcohol

protonation of the oxygen

electrophile

back-side attack by the nucleophile

Secondary and tertiary alcohols undergo S_N1 reactions with hydrogen halides.

Primary alcohols undergo S_N2 reactions with hydrogen halides.

- The acid protonates the most basic atom in the reactant.
- The nucleophile attacks the back side of the carbon and displaces the leaving group.

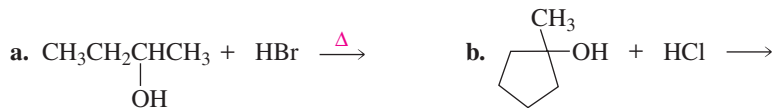
A β-carbon is the carbon adjacent to the carbon that is attached to the leaving group.

Only a substitution product is obtained. No elimination product is formed because the halide ion, although a good nucleophile, is a weak base, and a strong base is required to remove a hydrogen from a β-carbon in an E2 reaction (Section 8.7).

PROBLEM 5♦

What is the major product of each of the following reactions?

a. $CH_3CH_2CHCH_3$ (with OH on C-2) + HBr $\xrightarrow{\Delta}$

b. 1-methylcyclopentanol (CH_3 and $-OH$ on the same ring carbon) + HCl $\longrightarrow$

PROBLEM 6 Solved

Using the pK_a values of the conjugate acids of the leaving groups (the pK_a of HBr is -9, the pK_a of H_2O is 15.7, and the pK_a of H_3O^+ is -1.7), explain the difference in reactivity in substitution reactions between

a. CH_3Br and CH_3OH.

b. $CH_3\overset{+}{O}H_2$ and CH_3OH.

Solution to 6a The conjugate acid of the leaving group of CH_3Br is HBr; the conjugate acid of the leaving group of CH_3OH is H_2O. Because HBr is a much stronger acid (pK_a = -9) than H_2O (pK_a = 15.7), Br^- is a much weaker base than HO^-. (Recall that the stronger the acid, the weaker its conjugate base.) Therefore, Br^- is a much better leaving group than HO^-, causing CH_3Br to be much more reactive than CH_3OH in a substitution reaction.

PROBLEM 7 Solved

Show how 1-butanol can be converted into the following compounds:

a. $CH_3CH_2CH_2CH_2OCH_3$

b. $CH_3CH_2CH_2CH_2O\overset{O}{\overset{\|}{C}}CH_2CH_3$

c. $CH_3CH_2CH_2CH_2NHCH_2CH_3$

d. $CH_3CH_2CH_2CH_2C{\equiv}N$

Solution to 7a Because the OH group of 1-butanol is too basic to allow the alcohol to undergo a substitution reaction with CH_3O^-, the alcohol must first be converted into an alkyl halide. The alkyl halide has a leaving group that can be substituted by CH_3O^-, the nucleophile required to obtain the desired product.

$$CH_3CH_2CH_2CH_2OH \xrightarrow[\Delta]{HBr} CH_3CH_2CH_2CH_2Br \xrightarrow{CH_3O^-} CH_3CH_2CH_2CH_2OCH_3$$

PROBLEM 8♦

The observed relative reactivities of primary, secondary, and tertiary alcohols with a hydrogen halide are 3° > 2° > 1°. If secondary alcohols were to undergo an S_N2 reaction rather than an S_N1 reaction with a hydrogen halide, what would be the relative reactivities of the three classes of alcohols?

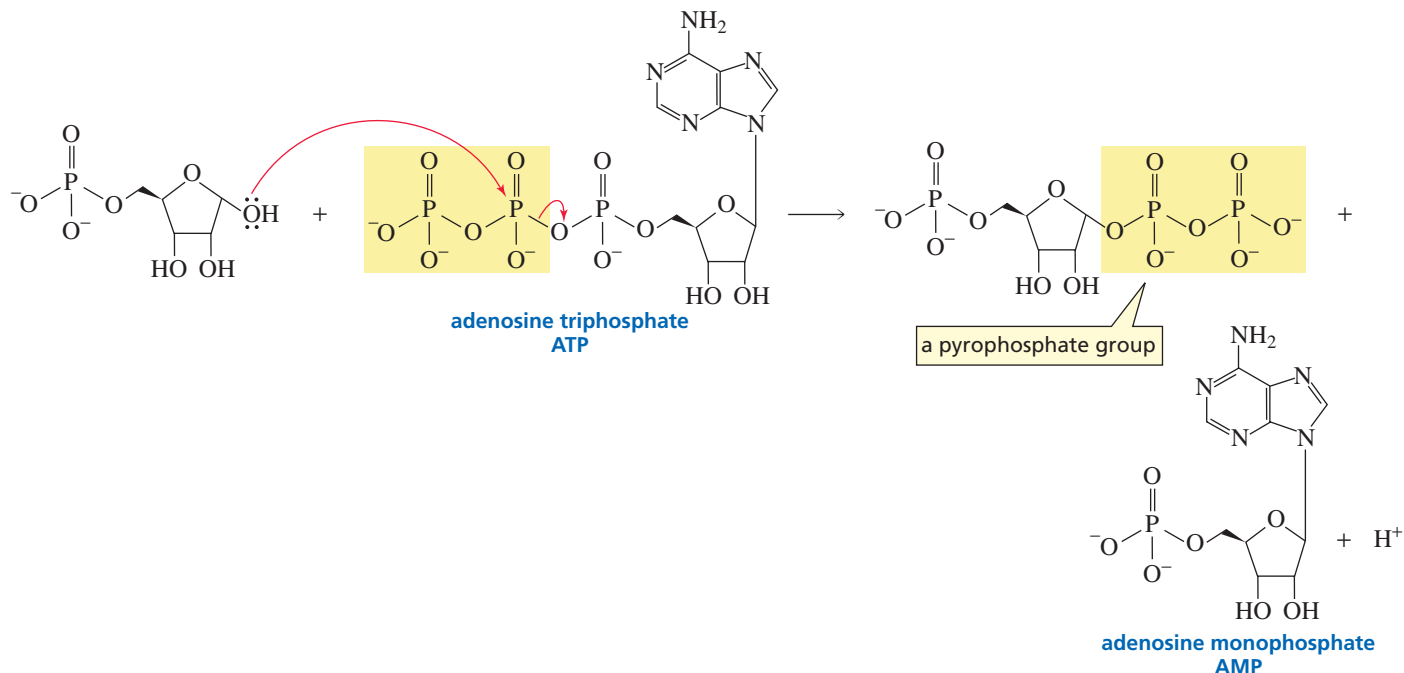
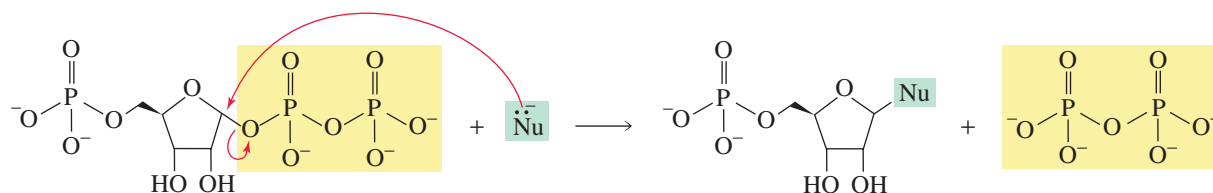
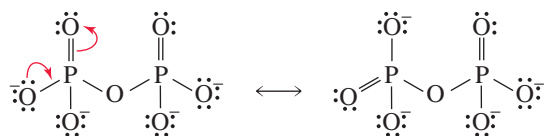
9.3 ACTIVATING AN OH GROUP FOR NUCLEOPHILIC SUBSTITUTION IN A CELL

Cells cannot activate an OH group for nucleophilic substitution by protonating it (Section 9.2). First of all, a high concentration of a strong acid, such as HBr, is not available to a cell. (Physiological pH is 7.4.) Furthermore, the nucleophiles in the cell that react with activated OH groups are often amines, which would be protonated in strongly acidic solutions and, therefore, would not be nucleophiles.

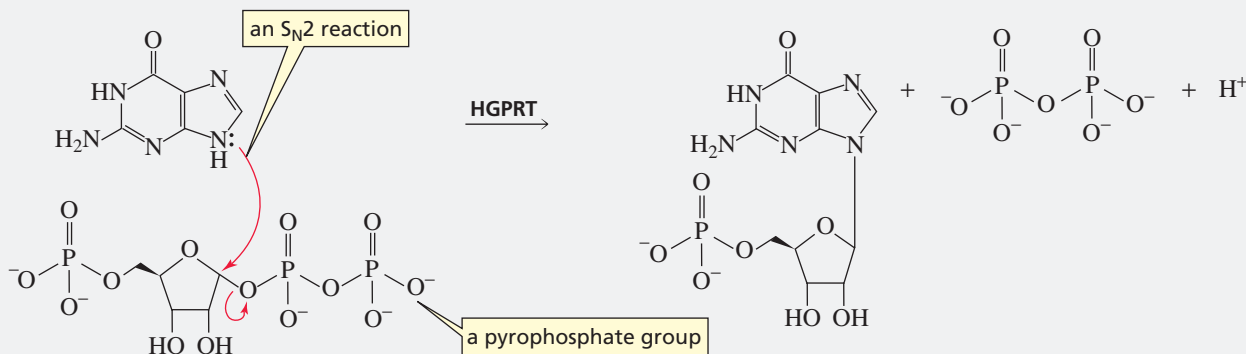
The compound shown here (with several OH groups) is a metabolite for the synthesis of many important biological compounds. One of its OH groups is activated by being converted to a **pyrophosphate group**. The pyrophosphate group is formed by an S_N2 reaction with adenosine triphosphate (ATP).

adenosine triphosphate
ATP

a pyrophosphate group

adenosine monophosphate
AMP

The activated compound can now react with a variety of nucleophiles. This reaction occurs in the synthesis of the nucleotides needed for the synthesis of DNA and RNA, in the synthesis of several amino acids, in the synthesis of polysaccharides, and in the synthesis of other important biological compounds.

Pyrophosphate is a good leaving group because the electrons released when the group departs can be delocalized onto an oxygen. Recall that electron delocalization stabilizes a molecule, and stable bases are weak bases.

Why nature chose phosphorus-containing compounds for activating groups is explained in Section 19.1.

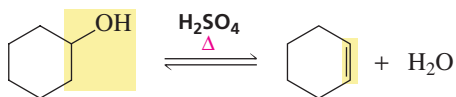
The Inability to Perform an S_N2 Reaction Causes a Severe Clinical Disorder

In the human body, an enzyme called HGPRT catalyzes the nucleophilic substitution reaction shown here.

A severe deficiency in HGPRT causes Lesch-Nyhan syndrome. This congenital defect occurs mostly in males and has tragic symptoms—namely, crippling arthritis and severe malfunctions in the nervous system such as mental retardation, highly aggressive and destructive behavior, and self-mutilation. Children with Lesch-Nyhan syndrome have such a compulsive urge to bite their fingers and lips that they have to be restrained. Fortunately, HGPRT deficiencies in fetal cells can be detected by amniocentesis. The condition occurs in 1 in 380,000 live births.

9.4 ELIMINATION REACTIONS OF ALCOHOLS: DEHYDRATION

An alcohol can undergo an elimination reaction by losing an OH from one carbon and an H from an adjacent carbon. The product of the reaction is an alkene. Overall, this amounts to the elimination of a molecule of water. Loss of water from a molecule is called **dehydration.**

Dehydration of an alcohol requires an acid catalyst and heat. Sulfuric acid (H_2SO_4) is the most commonly used acid catalyst. Recall that a catalyst increases the rate of a reaction but is not consumed during the course of a reaction (Section 5.10).

acid-catalyzed dehydration

The E1 Dehydration of Secondary and Tertiary Alcohols

The mechanism for acid-catalyzed dehydration depends on the structure of the alcohol; dehydrations of secondary and tertiary alcohols are E1 reactions.

MECHANISM FOR THE E1 DEHYDRATION OF AN ALCOHOL

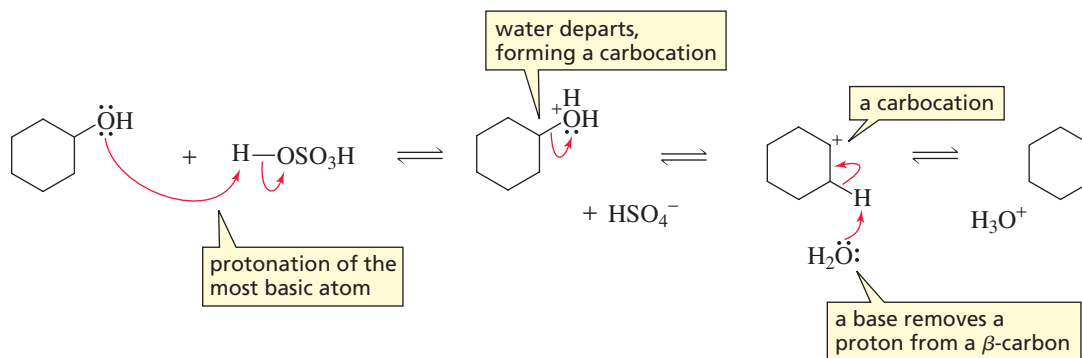
(cyclohexanol) + $H{-}OSO_3H$ ⇌ (protonated cyclohexanol, $\overset{+}{O}H_2$) + HSO_4^- ⇌ (cyclohexyl carbocation) ⇌ (cyclohexene) + H_3O^+

$H_2\ddot{O}$:

protonation of the most basic atom

water departs, forming a carbocation

a carbocation

a base removes a proton from a β-carbon

- The acid protonates the most basic atom in the reactant. As we saw earlier, protonation converts the very poor leaving group (HO^-) into a good leaving group (H_2O).
- Water departs, leaving behind a carbocation.
- A base in the reaction mixture (water is the base that is present in the highest concentration) removes a proton from a β-carbon (a carbon adjacent to the positively charged carbon), forming an alkene and regenerating the acid catalyst. Notice that the dehydration reaction is an E1 reaction of a protonated alcohol.

Dehydration of secondary and tertiary alcohols are E1 reactions.

When acid-catalyzed dehydration leads to more than one elimination product, the major product will be the more stable alkene—that is, the one obtained by removing a proton from the β-carbon bonded to the fewest hydrogens (Section 8.8). The more stable alkene is the major product because it has the more stable transition state leading to its formation (Figure 9.1).

$$CH_3C(CH_3)(OH)CH_2CH_3 \xrightleftharpoons[\Delta]{H_2SO_4} \underset{84\%}{CH_3C(CH_3){=}CHCH_3} + \underset{16\%}{CH_2{=}C(CH_3)CH_2CH_3} + H_2O$$

$$\text{1-methylcyclohexanol } (H_3C,\ OH) \xrightleftharpoons[\Delta]{H_2SO_4} \underset{93\%}{\text{1-methylcyclohexene } (CH_3)} + \underset{7\%}{\text{methylenecyclohexane } (CH_2)} + H_2O$$

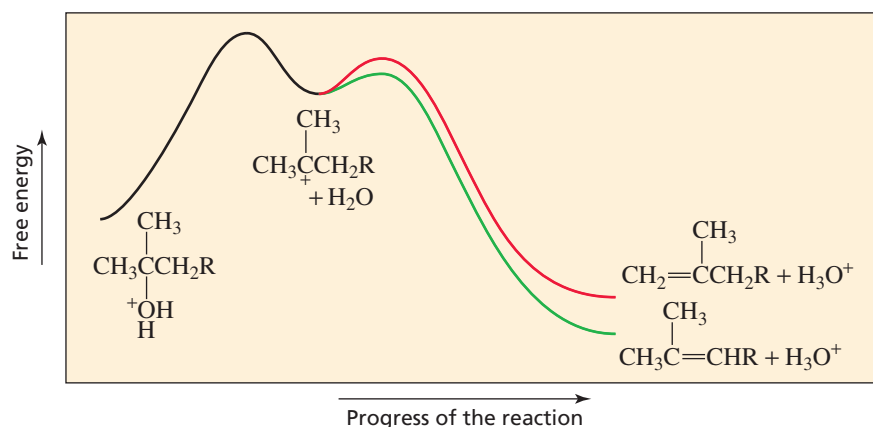
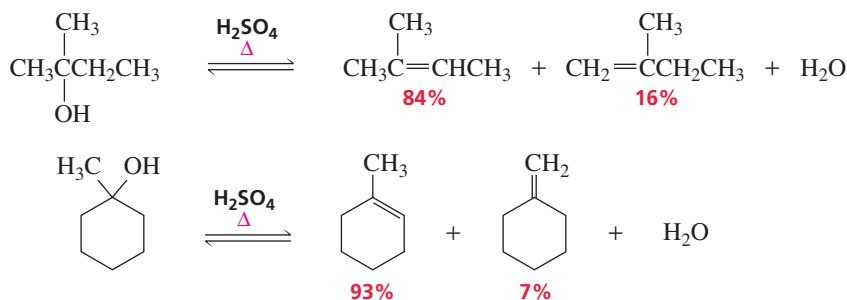
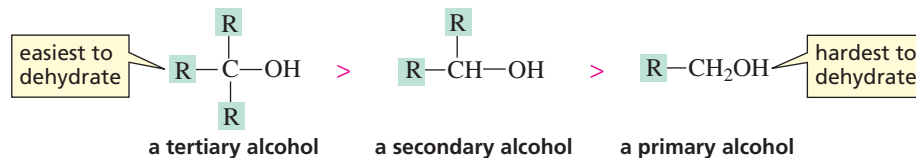



Figure 9.1
The more stable alkene is the major product obtained from the dehydration of an alcohol because the transition state leading to its formation is more stable (indicated by the green line), allowing it to be formed more rapidly.

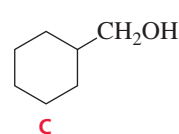
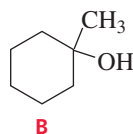
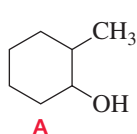
Because the rate-determining step in the dehydration of a secondary or a tertiary alcohol is formation of a carbocation intermediate, the rate of dehydration depends on the ease with which the carbocation is formed: tertiary alcohols are the easiest to dehydrate because tertiary carbocations are more stable and are therefore more easily formed than secondary and primary carbocations (Section 6.2).

relative ease of dehydration

easiest to dehydrate: $R_3C{-}OH$ (a tertiary alcohol) > $R_2CH{-}OH$ (a secondary alcohol) > $R{-}CH_2OH$ (a primary alcohol): hardest to dehydrate

PROBLEM 9♦

Which of the following alcohols would dehydrate the fastest when heated with acid?

A (2-methylcyclohexanol: CH_3, OH) B (1-methylcyclohexanol: CH_3, OH) C (cyclohexylmethanol: CH_2OH)

The E2 Dehydration of Primary Alcohols

Dehydration of a primary alcohol is an E2 reaction.

Alcohols undergo S_N1/E1 reactions unless they have to form a primary carbocation, in which case they undergo S_N2/E2 reactions.

While the dehydration of a secondary or a tertiary alcohol is an E1 reaction, the dehydration of a primary alcohol is an E2 reaction, because primary carbocations are extremely unstable. Any base (B:) in the reaction mixture (ROH, ROR, H_2O, or HSO_4^-) can remove the proton in the elimination reaction. The reaction also forms an ether in a competing S_N2 reaction, since primary alcohols are the ones most likely to form substitution products under S_N2/E2 conditions (Section 8.11).

MECHANISM FOR THE E2 DEHYDRATION OF A PRIMARY ALCOHOL AND FOR THE COMPETING S_N2 REACTION

$$CH_3CH_2\ddot{O}H + H{-}OSO_3H \rightleftharpoons CH_2(H){-}CH_2{-}\overset{+}{O}H_2 \xrightleftharpoons{E2} CH_2{=}CH_2 + H_2O + HB^+$$

protonation of the most basic atom

B: + HSO_4^-

base removes a proton from a β-carbon

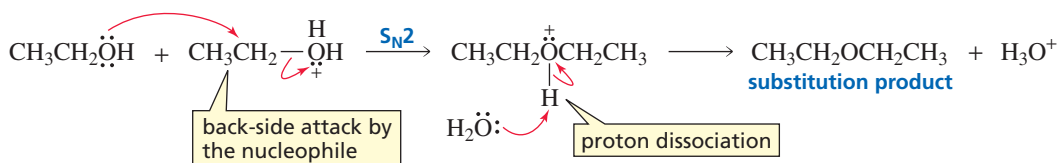
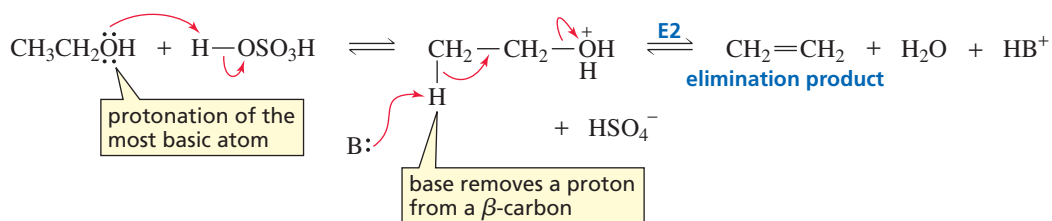
elimination product

$$CH_3CH_2\ddot{O}H + CH_3CH_2{-}\overset{+}{O}H_2 \xrightarrow{S_N2} CH_3CH_2\overset{+}{O}(H)CH_2CH_3 \longrightarrow CH_3CH_2OCH_2CH_3 + H_3O^+$$

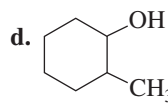
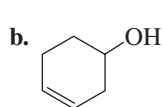
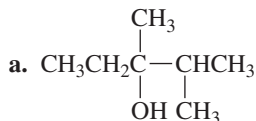
back-side attack by the nucleophile

$H_2\ddot{O}$:

proton dissociation

substitution product

PROBLEM 10

Draw the major elimination product obtained when each of the following alcohols is heated in the presence of H_2SO_4:

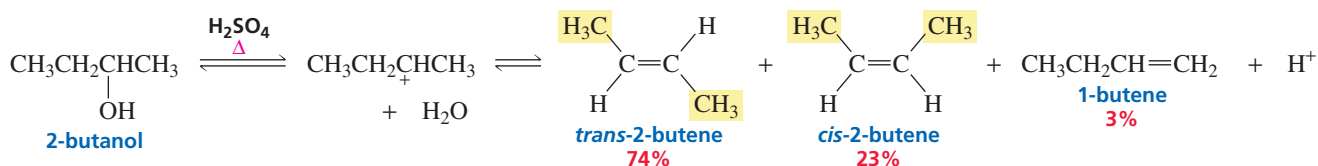
a. $CH_3CH_2C(CH_3)(OH){-}CH(CH_3)CH_3$ **b.** cyclohex-3-enol (OH) **c.** $CH_2{=}CHCH_2CH_2OH$ **d.** 2-methylcyclohexanol (OH, CH_3)

PROBLEM 11

Heating an alcohol with sulfuric acid is a good way to prepare a symmetrical ether such as diethyl ether.

a. Explain why it is not a good way to prepare an unsymmetrical ether such as ethyl propyl ether.
b. How would you synthesize ethyl propyl ether?

The Stereochemistry of the Dehydration Reaction

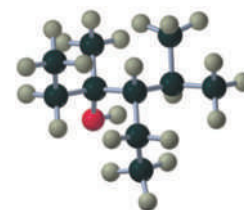
The products obtained from the E1 dehydration of an alcohol are identical to the products obtained from the E1 reaction of an alkyl halide. That is, both the *E* and *Z* stereoisomers are obtained as products, but the major product is the stereoisomer in which the larger group on each of the sp^2 carbons are on opposite sides of the double bond. Because that stereoisomer is more stable, it is formed more rapidly (Section 8.8).

$$\underset{\text{2-butanol}}{CH_3CH_2CH(OH)CH_3} \underset{\Delta}{\overset{H_2SO_4}{\rightleftharpoons}} CH_3CH_2\overset{+}{C}HCH_3 + H_2O \rightleftharpoons \underset{\substack{\textit{trans}\text{-2-butene} \\ 74\%}}{(H_3C)(H)C{=}C(H)(CH_3)} + \underset{\substack{\textit{cis}\text{-2-butene} \\ 23\%}}{(H_3C)(H)C{=}C(H)(CH_3)} + \underset{\substack{\text{1-butene} \\ 3\%}}{CH_3CH_2CH{=}CH_2} + H^+$$

PROBLEM 12♦

What stereoisomers are formed from the acid-catalyzed dehydration of 3,4-dimethyl-3-hexanol? Which stereoisomer is the major product?

PROBLEM 13♦

Suppose the compound shown in the margin is heated in the presence of H_2SO_4.

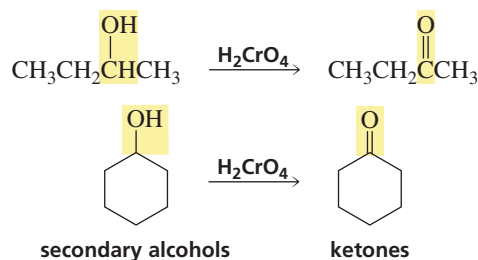
a. What constitutional isomer would be produced in greatest yield?
b. What stereoisomer would be produced in greater yield?

9.5 OXIDATION OF ALCOHOLS

We have seen that a **reduction reaction** *increases* the number of C—H bonds in a compound (Section 5.6). Oxidation is the reverse of reduction. Therefore, an **oxidation reaction** *decreases* the number of C—H bonds (or increases the number of C—O bonds).

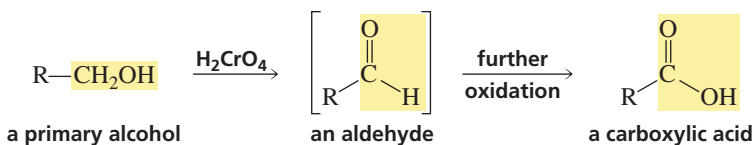
A variety of reagents are available that oxidize alcohols. For many years, a commonly used reagent was chromic acid (H_2CrO_4). Notice that *secondary alcohols* are oxidized to *ketones*.

$$CH_3CH_2CH(OH)CH_3 \xrightarrow{H_2CrO_4} CH_3CH_2C(=O)CH_3$$

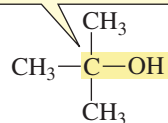
$$\text{cyclohexanol} \xrightarrow{H_2CrO_4} \text{cyclohexanone}$$

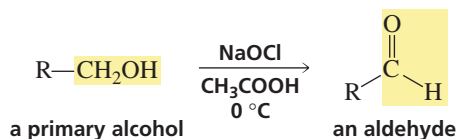
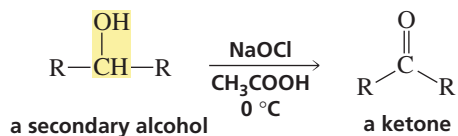
secondary alcohols **ketones**

Primary alcohols are initially oxidized to *aldehydes* by chromic acid. The reaction, however, does not stop at the aldehyde. Instead, the aldehyde is further oxidized to a *carboxylic acid*.

$$R{-}CH_2OH \xrightarrow{H_2CrO_4} \left[R{-}\overset{O}{\overset{\|}{C}}{-}H\right] \xrightarrow[\text{oxidation}]{\text{further}} R{-}\overset{O}{\overset{\|}{C}}{-}OH$$

a primary alcohol — an aldehyde — a carboxylic acid

Notice that, in the oxidation of both primary and a secondary alcohols, a hydrogen is removed from the carbon to which the OH is attached. The carbon bearing the OH group in a tertiary alcohol is not bonded to a hydrogen, so its OH group cannot be oxidized to a carbonyl (C=O) group.

this C is not bonded to an H, so the alcohol cannot be oxidized to a carbonyl compound

$$CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}OH$$

a tertiary alcohol

Because of the toxicity of chromium-based reagents, other reagents for the oxidation of alcohols have been developed. One of the more common is hypochlorous acid (HOCl). Hypochlorous acid is unstable, so it is generated in situ (in the reaction mixture) by an acid–base reaction between H^+ and ^-OCl (using CH_3COOH and NaOCl). Secondary alcohols are oxidized to ketones and primary alcohols are oxidized to aldehydes.

Secondary alcohols are oxidized to ketones.

Primary alcohols are oxidized to aldehydes.

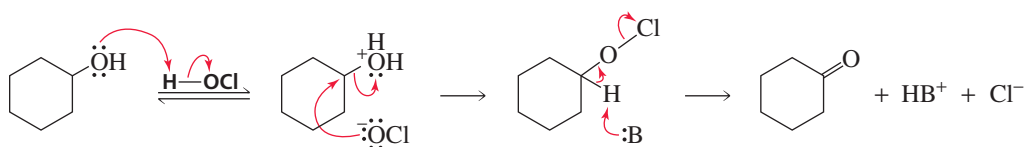
$$R{-}\overset{OH}{\overset{|}{C}H}{-}R \xrightarrow[\substack{CH_3COOH\\ 0\,°C}]{NaOCl} R{-}\overset{O}{\overset{\|}{C}}{-}R$$

a secondary alcohol — a ketone

$$R{-}CH_2OH \xrightarrow[\substack{CH_3COOH\\ 0\,°C}]{NaOCl} R{-}\overset{O}{\overset{\|}{C}}{-}H$$

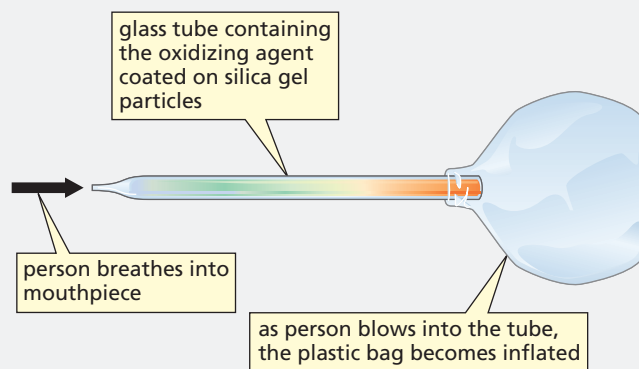
a primary alcohol — an aldehyde

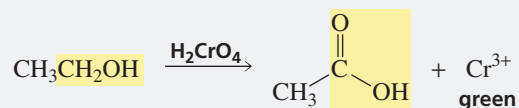
MECHANISM FOR THE OXIDATION OF AN ALCOHOL BY HOCl

Cyclohexanol + H—OCl ⇌ protonated cyclohexanol ($^+$OH$_2$) + $^-$:OCl: → cyclohexyl–O–Cl (with H, :B) → cyclohexanone + HB^+ + Cl^-

- The acid protonates the oxygen, the most basic atom in the alcohol.
- Because the reaction is not heated, water does not leave spontaneously but must be displaced by a hypochlorite ion in an S_N2 reaction.
- A base in the reaction mixture removes a proton from the carbon bonded to the O—Cl group and the very weak O—Cl bond breaks.

Blood Alcohol Content

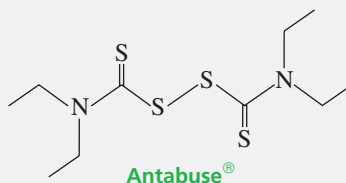
As blood passes through the arteries in our lungs, an equilibrium is established between the alcohol in our blood and the alcohol in our breath. Therefore, if the concentration of one is known, then the concentration of the other can be estimated.

The test that law enforcement agencies use to approximate a person's blood alcohol level is based on the oxidation of breath ethanol. An oxidizing agent impregnated onto an inert material is enclosed within a sealed glass tube. When the test is to be administered, the ends of the tube are broken off and replaced with a mouthpiece at one end and a balloon-type bag at the other. The person being tested blows into the mouthpiece until the bag is filled with air.

Any breath ethanol is oxidized as it passes through the column. When ethanol is oxidized, the oxidizing agent is reduced to green chromic ion. The greater the concentration of breath alcohol, the farther the green color spreads through the tube.

$$CH_3CH_2OH \xrightarrow{H_2CrO_4} CH_3COOH + \underset{\text{green}}{Cr^{3+}}$$

If the person fails this test—determined by the extent to which the green color spreads through the tube—a more accurate Breathalyzer™ test is administered. The Breathalyzer test also depends on the oxidation of breath ethanol, but it provides more accurate results because it is quantitative. In this test, a known volume of breath is bubbled through a solution of chromic acid, and the concentration of the green chromic ion is measured precisely with a spectrophotometer (Section 10.18).

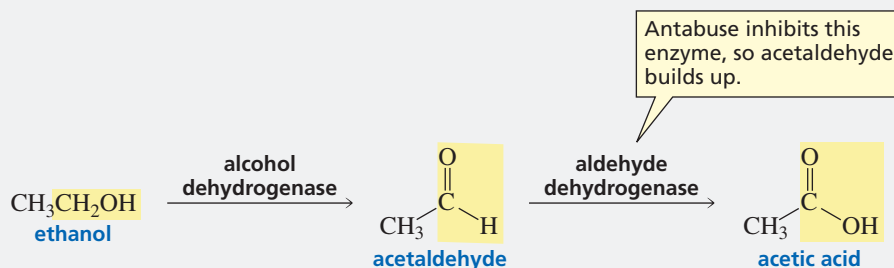
Treating Alcoholism with Antabuse

Disulfiram, most commonly known as Antabuse, is used to treat alcoholism. It causes violently unpleasant effects if ethanol is consumed within two days after taking the drug.

$$(CH_3CH_2)_2N-C(=S)-S-S-C(=S)-N(CH_2CH_3)_2$$

Antabuse®

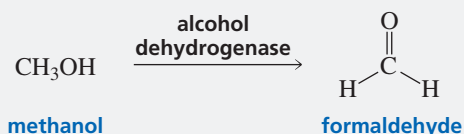
Antabuse works by inhibiting aldehyde dehydrogenase, the enzyme responsible for oxidizing acetaldehyde (a product of ethanol metabolism) to acetic acid. This causes a buildup of acetaldehyde. It is the acetaldehyde that causes the unpleasant physiological effects of intoxication: intense flushing, nausea, dizziness, sweating, throbbing headaches, decreased blood pressure, and, ultimately, shock. Consequently, Antabuse should be taken only under strict medical supervision.

$$\underset{\text{ethanol}}{CH_3CH_2OH} \xrightarrow{\text{alcohol dehydrogenase}} \underset{\text{acetaldehyde}}{CH_3CHO} \xrightarrow{\text{aldehyde dehydrogenase}} \underset{\text{acetic acid}}{CH_3COOH}$$

Antabuse inhibits this enzyme, so acetaldehyde builds up.

In some people, aldehyde dehydrogenase does not function properly even under normal circumstances. Their symptoms in response to ingesting alcohol are nearly the same as those of individuals who are medicated with Antabuse.

Methanol Poisoning

In addition to oxidizing ethanol to acetaldehyde, alcohol dehydrogenase can oxidize methanol to formaldehyde. Formaldehyde is damaging to many tissues, and since eye tissue is particularly sensitive, methanol ingestion can cause blindness.

$$\underset{\text{methanol}}{CH_3OH} \xrightarrow{\text{alcohol dehydrogenase}} \underset{\text{formaldehyde}}{H-\overset{\overset{\large O}{\|}}{C}-H}$$

If methanol is ingested, the patient is given ethanol intravenously for several hours. Ethanol competes with methanol for binding at the active site of the enzyme. Binding ethanol minimizes the amount of methanol that can be bound, which minimizes the amount of formaldehyde that can be formed. So ethanol is given to the patient until all the ingested methanol has been excreted in the urine.

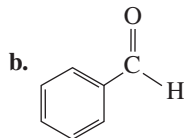
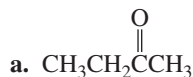
PROBLEM 14♦

What product will be obtained from the reaction of each of the following alcohols with HOCl?

a. 3-pentanol **b.** 2-methyl-2-pentanol **c.** 1-pentanol

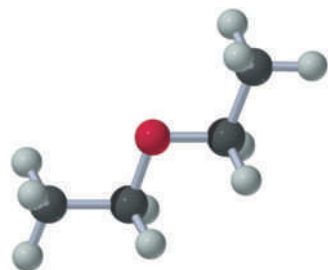
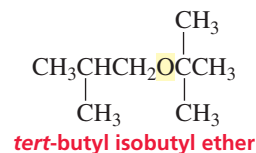
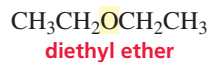
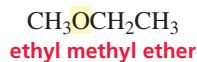
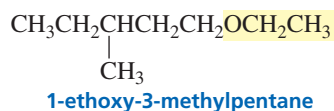
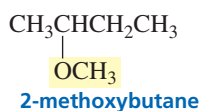
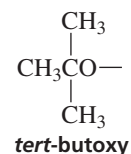
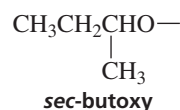
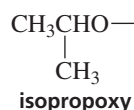
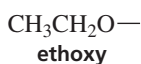
PROBLEM 15♦

What alcohol would be required to synthesize each of the following compounds?

a. $CH_3CH_2\overset{\overset{O}{\|}}{C}CH_3$ **b.** (benzene ring)$-\overset{\overset{O}{\|}}{C}-H$ **c.** $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H$

9.6 NOMENCLATURE OF ETHERS

dimethyl ether

diethyl ether

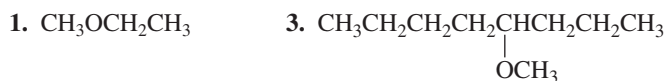
An **ether** is a compound in which an oxygen is bonded to two alkyl substituents. The common name of an ether consists of the names of the two alkyl substituents (in alphabetical order), followed by the word "ether." The smallest ethers are almost always named by their common names.

The IUPAC system names an ether as an alkane with an RO substituent. The substituents are named by replacing the "yl" ending in the name of the alkyl substituent with "oxy."

PROBLEM 16♦

a. What is each ether's systematic name?

1. $CH_3OCH_2CH_3$

3. $CH_3CH_2CH_2CH_2CHCH_2CH_2CH_3$ (with OCH_3 on the CH)

2. $CH_3CH_2OCH_2CH_3$

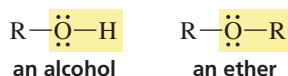
4. $CH_3CH_2CH_2OCH_2CH_2CH_2CH_3$

b. Do all of these ethers have common names?

c. What are their common names?

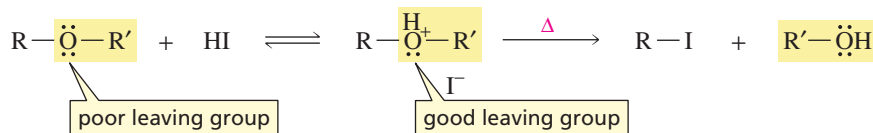
9.7 NUCLEOPHILIC SUBSTITUTION REACTIONS OF ETHERS

The OR group of an ether and the OH group of an alcohol have nearly the same basicity, because the conjugate acids of these two groups have similar pK_a values. (The pK_a of CH_3OH is 15.5 and the pK_a of H_2O is 15.7.) Both groups are strong bases, so both are very poor leaving groups. Consequently, ethers, like alcohols, need to be activated before they can undergo a nucleophilic substitution reaction.

$$R{-}\ddot{O}{-}H \qquad R{-}\ddot{O}{-}R$$

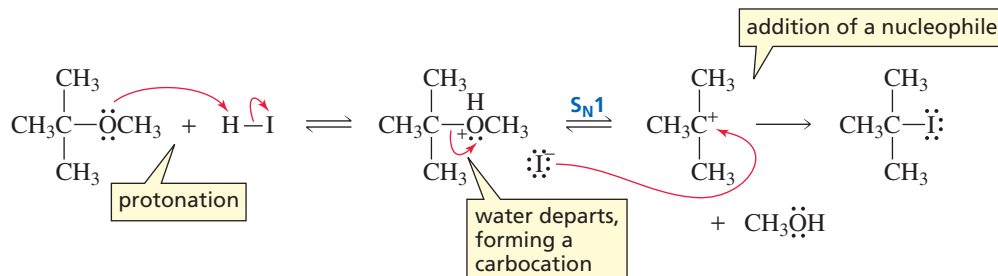
an alcohol — an ether

Like alcohols, ethers can be activated by protonation. Ethers, therefore, can undergo nucleophilic substitution reactions with HBr or HI. The reaction of ethers with hydrogen halides, like the reactions of alcohols with hydrogen halides, is slow. The reaction mixture must be heated to cause the reaction to occur at a reasonable rate.

$$R{-}\ddot{O}{-}R' + HI \rightleftharpoons R{-}\overset{H}{O^+}{-}R' \;\; I^- \xrightarrow{\Delta} R{-}I + R'{-}\ddot{O}H$$

poor leaving group — good leaving group

What happens *after* the ether is protonated depends on the structure of the ether. If departure of ROH creates a relatively stable carbocation (such as a tertiary carbocation), the ROH group will leave. In other words, an S_N1 reaction will occur.

MECHANISM FOR ETHER CLEAVAGE: AN S_N1 REACTION

$$(CH_3)_3C{-}\ddot{O}CH_3 + H{-}I \rightleftharpoons (CH_3)_3C{-}\overset{+}{O}(H)CH_3 \;\; :\ddot{I}:^- \underset{S_N1}{\rightleftharpoons} (CH_3)_3C^+ + CH_3\ddot{O}H \longrightarrow (CH_3)_3C{-}\ddot{I}:$$

protonation — water departs, forming a carbocation — addition of a nucleophile

- The acid protonates the oxygen, thereby converting the very basic RO^- leaving group into the less basic ROH leaving group.
- The leaving group departs, forming a carbocation.
- The halide ion combines with the carbocation.

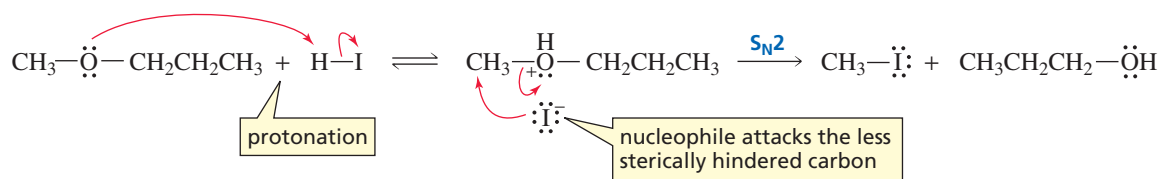
Ethers are cleaved by an S_N1 reaction unless the instability of the carbocation requires the cleavage to be an S_N2 reaction.

However, if departure of the ROH group would create an unstable carbocation (such as a methyl or primary carbocation), the ROH group will not be able to leave. It has to be displaced by the halide ion. In other words, an S_N2 reaction will occur.

MECHANISM FOR ETHER CLEAVAGE: AN S_N2 REACTION

$$CH_3-\ddot{O}-CH_2CH_2CH_3 + H-I \rightleftharpoons CH_3-\overset{H}{\overset{+}{O}}-CH_2CH_2CH_3 \xrightarrow{S_N2} CH_3-\ddot{I}: + CH_3CH_2CH_2-\ddot{O}H$$

protonation

nucleophile attacks the less sterically hindered carbon

- Protonation converts the very basic RO^- leaving group into the less basic ROH leaving group.
- The halide ion preferentially attacks the less sterically hindered of the two alkyl groups.

Because hydrogen halides are the only reagents that react with ethers, ethers are frequently used as solvents. Some common ether solvents are shown in Table 9.1.

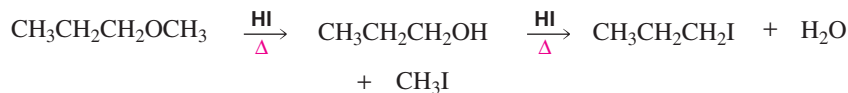
Table 9.1 Some Ethers Are Used as Solvents

diethyl ether "ether"	tetrahydrofuran THF	tetrahydropyran THP	1,4-dioxane	1,2-dimethoxyethane DME	*tert*-butyl methyl ether MTBE

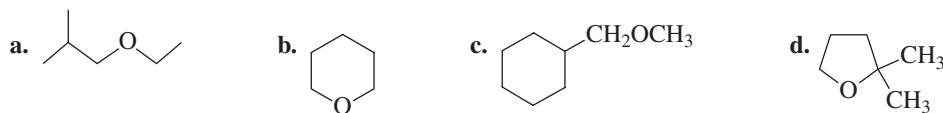
PROBLEM 17 Solved

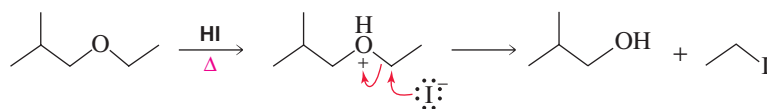
Explain why methyl propyl ether forms both methyl iodide and propyl iodide when it is heated with excess HI.

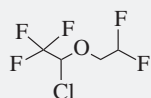
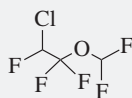
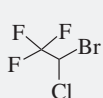
Solution We just saw (on the top of this page) that the S_N2 reaction of methyl propyl ether with an equivalent amount of HI forms methyl iodide and propyl alcohol because the methyl group is less sterically hindered than the propyl group to attack by the iodide ion. When there is excess HI, the alcohol product of this first reaction can react with HI in another S_N2 reaction. Thus, the products are two alkyl iodides.

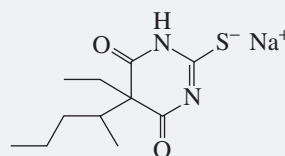
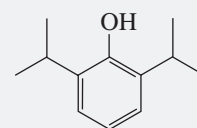
$$CH_3CH_2CH_2OCH_3 \xrightarrow[\Delta]{HI} CH_3CH_2CH_2OH + CH_3I \xrightarrow[\Delta]{HI} CH_3CH_2CH_2I + H_2O$$

PROBLEM 18 Solved

Draw the major products obtained from heating each of the following ethers with one equivalent of HI:

a. (isobutyl ethyl ether) **b.** (tetrahydropyran) **c.** CH_2OCH_3 (cyclohexylmethyl methyl ether) **d.** (2,2-dimethyltetrahydrofuran, CH_3, CH_3)

Solution to 18a The reaction takes place by an S_N2 pathway because neither alkyl group will form a relatively stable carbocation (both would be primary). The iodide ion attacks the carbon of the ethyl group because it is less sterically hindered than the carbon of the isobutyl group. Thus, the major products are ethyl iodide and isobutyl alcohol.

isobutyl ethyl ether $\xrightarrow[\Delta]{HI}$ protonated ether + $:\ddot{I}:^-$ $\longrightarrow$ isobutyl alcohol (OH) + ethyl iodide (I)

Anesthetics

Because diethyl ether (commonly known as ether) is a short-lived muscle relaxant, it was at one time widely used as an *inhalation anesthetic*. However, it takes effect slowly and has a slow and unpleasant recovery period, so over time other anesthetics, such as isoflurane, enflurane, and halothane, replaced it. Even so, diethyl ether is still used where trained anesthesiologists are scarce because it is the safest anesthetic for an untrained person to administer. Anesthetics interact with the nonpolar molecules of cell membranes, causing the membranes to swell, which interferes with their permeability.

"ether" isoflurane enflurane halothane

amputation of a leg without anesthetic in 1528

Sodium pentothal (also called thiopental sodium) is an *intravenous anesthetic*. The onset of anesthesia and the loss of consciousness occur within seconds of its administration. Care must be taken when administering sodium pentothal because the dose for effective anesthesia is 75% of the lethal dose. Because of this high level of toxicity, it cannot be used as the sole anesthetic but, instead, is generally used to induce anesthesia before an inhalation anesthetic is administered. Propofol, in contrast, has all the properties of the "perfect anesthetic": it can be administered as the sole anesthetic by intravenous drip, it has a rapid and pleasant induction period, and it has a wide margin of safety in trained hands. Recovery from the drug is also rapid and pleasant.

sodium pentothal
thiopental sodium

propofol
diprivan

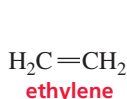
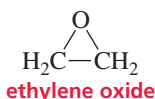
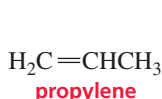
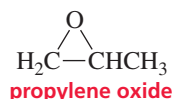
a painting showing the first use of anesthesia (ether) during surgery in 1846 at Massachusetts General Hospital by surgeon John Collins Warren

9.8 NUCLEOPHILIC SUBSTITUTION REACTIONS OF EPOXIDES

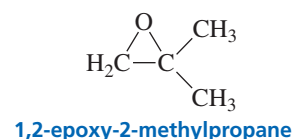
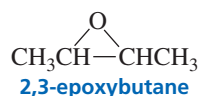
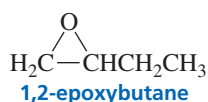
An **epoxide** is an ether in which the oxygen atom is incorporated into a three-membered ring. The common name of an epoxide is obtained by adding "oxide" to the common name of the corresponding alkene, assuming that the oxygen atom is where the π bond of an alkene would be. The simplest epoxide is ethylene oxide.

$H_2C{=}CH_2$ — ethylene

$H_2C{-}CH_2$ (with O bridging the two carbons) — ethylene oxide

$H_2C{=}CHCH_3$ — propylene

$H_2C{-}CHCH_3$ (with O bridging the two carbons) — propylene oxide

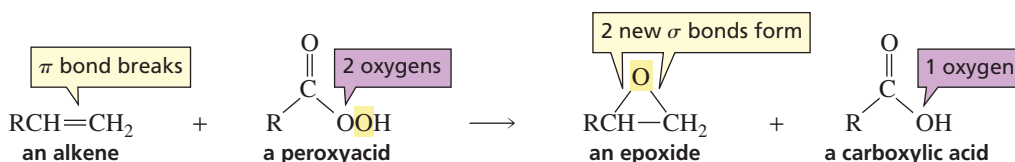
Alternatively, an epoxide can be named as an alkane, with an "epoxy" prefix that identifies the carbons to which the oxygen is attached.

1,2-epoxybutane   2,3-epoxybutane   1,2-epoxy-2-methylpropane

PROBLEM 19♦

Draw the structure of the following:

a. cyclohexene oxide **b.** 2,3-epoxy-2-methylpentane

An epoxide is formed from the reaction of an alkene with a *peroxyacid*. A **peroxyacid** is a carboxylic acid with an extra oxygen atom. It is this oxygen that is transferred to the alkene in order to from the epoxide. The reaction increases the number of C—O bonds in the reactant. It is, therefore, an oxidation reaction (Section 9.5).

$RCH{=}CH_2$ (an alkene; π bond breaks) + RCOOH (a peroxyacid; 2 oxygens) ⟶ an epoxide (2 new σ bonds form) + RCOOH (a carboxylic acid; 1 oxygen)

Although an epoxide and an ether have the same leaving group, epoxides are much more reactive than ethers in nucleophilic substitution reactions because the strain in their three-membered ring is relieved when the ring opens (Figure 9.2). Epoxides, therefore, undergo nucleophilic substitution reactions with a wide variety of nucleophiles.

ethylene oxide

$CH_3CH_2OCH_2CH_3$
diethyl ether

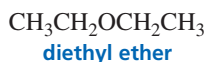
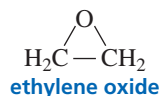
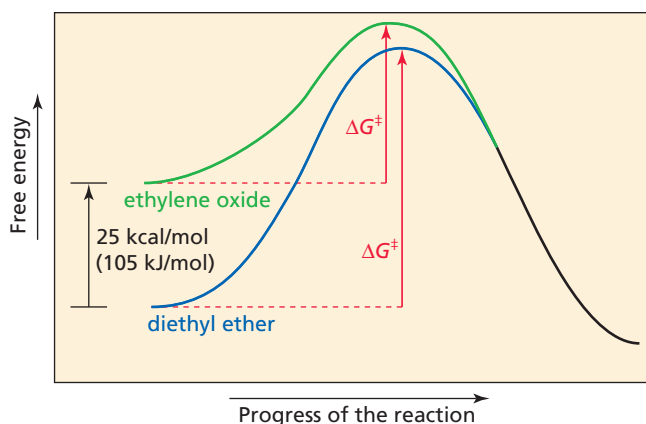



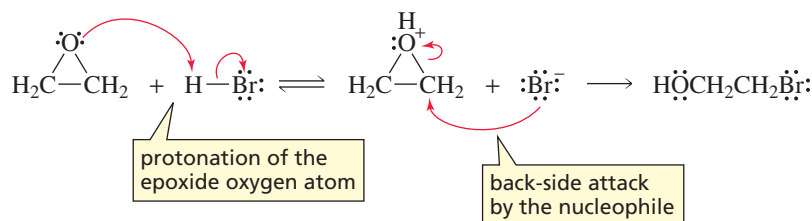
Figure 9.2
The reaction coordinate diagrams for nucleophilic attack of hydroxide ion on ethylene oxide and on diethyl ether. The greater reactivity of the epoxide is a result of the strain in the three-membered ring, which increases the epoxide's free energy.

Nucleophilic Substitution: Acidic Conditions

Epoxides, like other ethers, undergo substitution reactions with hydrogen halides. The mechanism of the reaction depends on whether it is carried out under acidic or neutral/basic conditions. Under acidic conditions, the mechanism shown next is followed.

MECHANISM FOR NUCLEOPHILIC SUBSTITUTION: ACIDIC CONDITIONS

ethylene oxide + H—Br ⇌ protonated epoxide + Br^- ⟶ $HOCH_2CH_2Br$

protonation of the epoxide oxygen atom

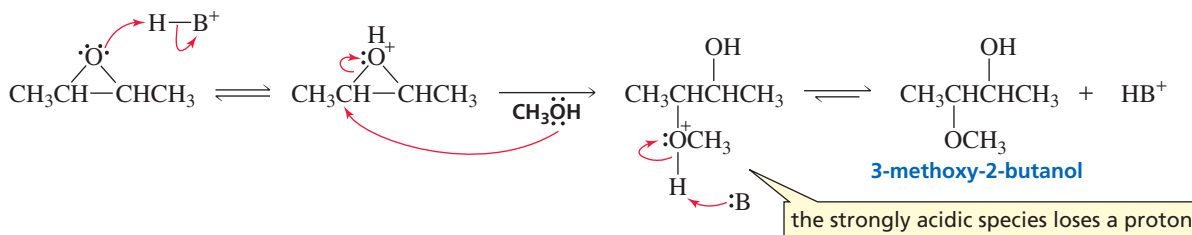
back-side attack by the nucleophile

- The acid protonates the oxygen of the epoxide.
- The protonated epoxide undergoes back-side attack by the halide ion.

Because epoxides are so much more reactive than ethers, the reaction takes place readily at room temperature, unlike the reaction of an ether with a hydrogen halide, which requires heat.

Protonated epoxides are so reactive that they can be opened by poor nucleophiles, such as H_2O and alcohols. (HB^+ is any acid in the solution and :B is any base.)

$CH_3CH{-}CHCH_3$ (epoxide) + $H{-}B^+$ ⇌ $CH_3CH{-}CHCH_3$ (protonated epoxide) $\xrightarrow{CH_3\ddot{O}H}$ $CH_3CH(OH)CH(\overset{+}{O}HCH_3)CH_3$ + :B ⇌ $CH_3CH(OH)CH(OCH_3)CH_3$ + HB^+

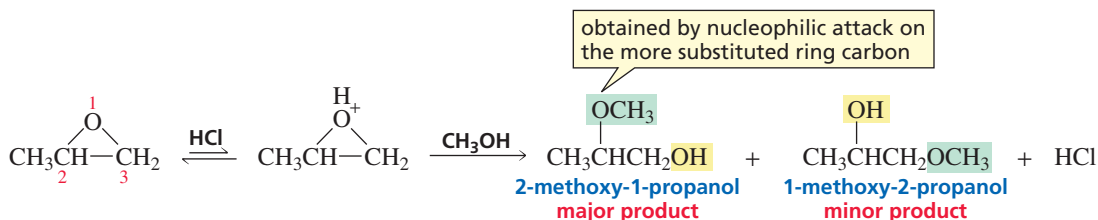
3-methoxy-2-butanol

the strongly acidic species loses a proton

If different substituents are attached to the two ring carbons of the protonated epoxide (and the nucleophile is something other than H_2O), the product obtained from nucleophilic attack on the 2-position of the ring will be different than that obtained from nucleophilic attack on the 3-position. The major product is the one resulting from nucleophilic attack on the *more substituted* carbon.

$CH_3CH{-}CH_2$ (epoxide; O 1, C 2, C 3) $\underset{}{\overset{HCl}{\rightleftharpoons}}$ $CH_3CH{-}CH_2$ (protonated epoxide) $\xrightarrow{CH_3OH}$ $CH_3CH(OCH_3)CH_2OH$ + $CH_3CH(OH)CH_2OCH_3$ + HCl

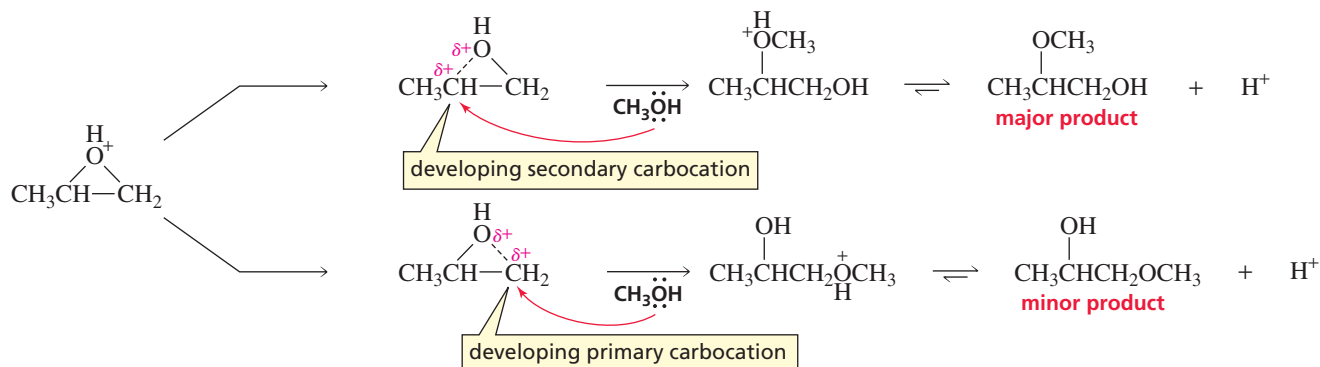
obtained by nucleophilic attack on the more substituted ring carbon

2-methoxy-1-propanol — major product

1-methoxy-2-propanol — minor product

The more substituted carbon is more likely to be attacked because, after the epoxide is protonated, it is so reactive that one of the C—O bonds begins to break even before the nucleophile has an opportunity to attack. As the bond starts to break, a partial positive charge develops on the carbon that is losing its share of oxygen's electrons. Therefore, the protonated epoxide breaks preferentially in the direction that puts the partial positive charge on the more substituted carbon, because a more substituted carbocation is more stable. (Recall that tertiary carbocations are more stable than secondary carbocations, which are more stable than primary carbocations.)

Protonated epoxide $CH_3CH{-}CH_2$:

→ $CH_3\overset{\delta+}{C}H{-}CH_2$ ($\overset{\delta+}{O}H$) — developing secondary carbocation $\xrightarrow{CH_3\ddot{O}H}$ $CH_3CH(\overset{+}{O}HCH_3)CH_2OH$ ⇌ $CH_3CH(OCH_3)CH_2OH$ + H^+ — major product

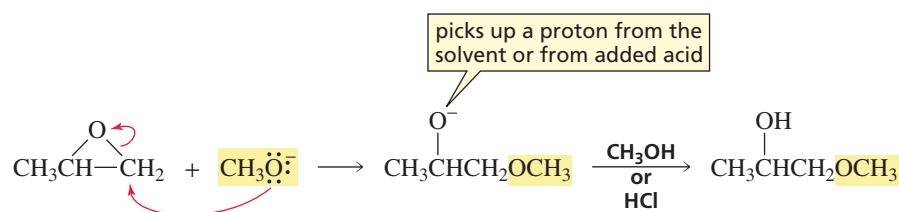
→ $CH_3CH{-}\overset{\delta+}{C}H_2$ ($\overset{\delta+}{O}H$) — developing primary carbocation $\xrightarrow{CH_3\ddot{O}H}$ $CH_3CH(OH)CH_2\overset{+}{O}HCH_3$ ⇌ $CH_3CH(OH)CH_2OCH_3$ + H^+ — minor product

The best way to describe the reaction is to say that it occurs by a pathway that is partially S_N1 and partially S_N2. It is not a pure S_N1 reaction because a carbocation intermediate is not fully formed; it is not a pure S_N2 reaction, either, because the leaving group begins to depart before the compound is attacked by the nucleophile.

Nucleophilic Substitution: Neutral or Basic Conditions

Although an ether must be protonated before it can undergo a nucleophilic substitution reaction (Section 9.7), the strain in the three-membered ring allows an epoxide to undergo nucleophilic substitution reactions without first being protonated (Figure 9.2). When a nucleophile attacks an unprotonated epoxide, the reaction is a pure S_N2 reaction.

MECHANISM FOR NUCLEOPHILIC SUBSTITUTION: NEUTRAL OR BASIC CONDITIONS

picks up a proton from the solvent or from added acid

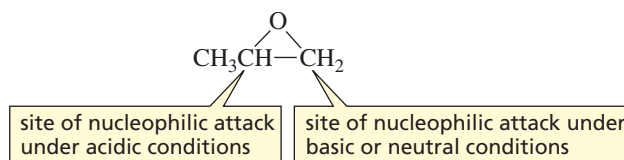
$$CH_3CH\overset{O}{—}CH_2 + CH_3\ddot{O}:^- \longrightarrow CH_3\underset{}{\overset{O^-}{C}}HCH_2OCH_3 \xrightarrow[\text{HCl}]{CH_3OH \text{ or}} CH_3\overset{OH}{C}HCH_2OCH_3$$

- The C—O bond does not begin to break until the carbon is attacked by the nucleophile. The nucleophile is more likely to attack the *less substituted* carbon because it is less sterically hindered.
- The alkoxide ion picks up a proton from the solvent or from an acid added after the reaction is over.

Under acidic conditions, the nucleophile preferentially attacks the more substituted ring carbon.

Thus, the site of nucleophilic attack on an unsymmetrical epoxide under neutral or basic conditions (when the epoxide *is not* protonated) is different from the site of nucleophilic attack under acidic conditions (when the epoxide *is* protonated).

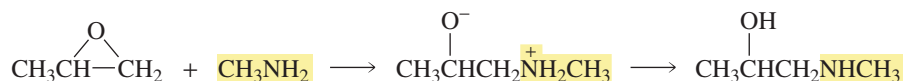
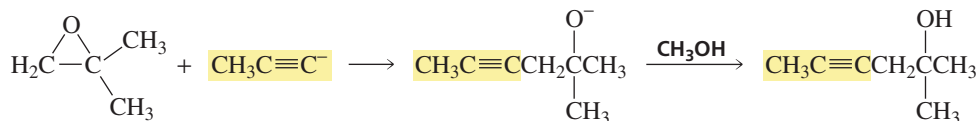
$$CH_3CH\overset{O}{—}CH_2$$

site of nucleophilic attack under acidic conditions

site of nucleophilic attack under basic or neutral conditions

Under neutral or basic conditions, the nucleophile preferentially attacks the less sterically hindered ring carbon.

Epoxides are useful reagents because they can react with a wide variety of nucleophiles, leading to the formation of a wide variety of products.

$$H_2C\overset{O}{—}C(CH_3)_2 + CH_3C{\equiv}C^- \longrightarrow CH_3C{\equiv}CCH_2\overset{O^-}{\underset{CH_3}{C}}CH_3 \xrightarrow{CH_3OH} CH_3C{\equiv}CCH_2\overset{OH}{\underset{CH_3}{C}}CH_3$$

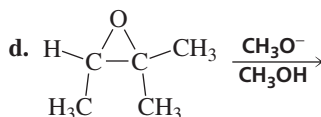
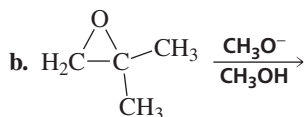
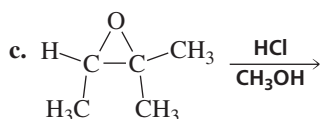
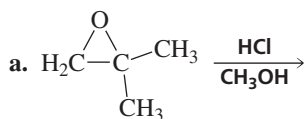
$$CH_3CH\overset{O}{—}CH_2 + CH_3NH_2 \longrightarrow CH_3\overset{O^-}{C}HCH_2\overset{+}{N}H_2CH_3 \longrightarrow CH_3\overset{OH}{C}HCH_2NHCH_3$$

PROBLEM 20♦

Draw the major product of each of the following reactions:

a. $H_2C-C(O)(CH_3)-CH_3$ (epoxide) $\xrightarrow[CH_3OH]{HCl}$

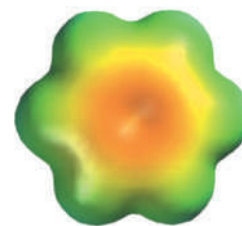
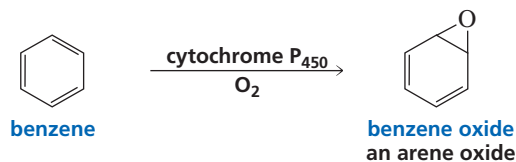
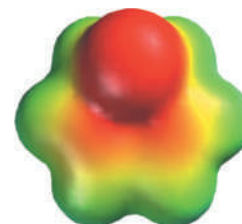
b. $H_2C-C(O)(CH_3)-CH_3$ (epoxide) $\xrightarrow[CH_3OH]{CH_3O^-}$

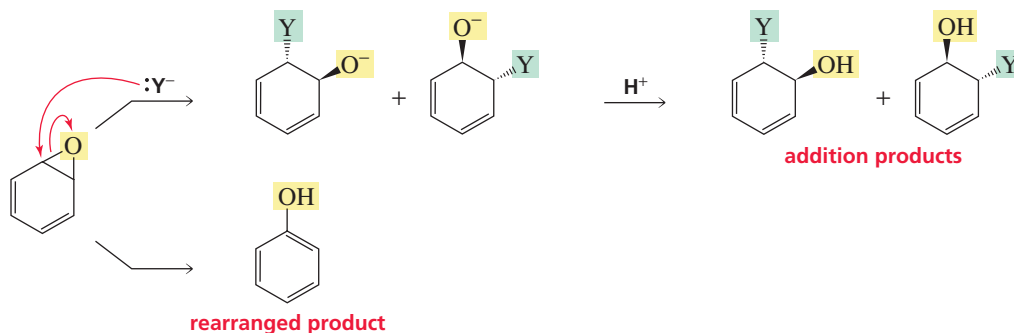
c. $H(H_3C)C-C(CH_3)-CH_3$ (epoxide, O bridging the two carbons) $\xrightarrow[CH_3OH]{HCl}$

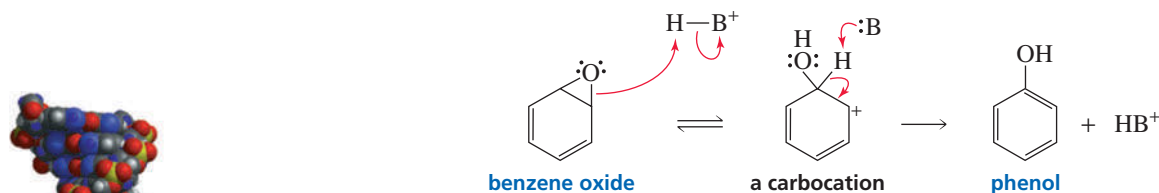
d. $H(H_3C)C-C(CH_3)-CH_3$ (epoxide, O bridging the two carbons) $\xrightarrow[CH_3OH]{CH_3O^-}$

PROBLEM 21♦

Would you expect the reactivity of a five-membered ring ether such as tetrahydrofuran (Table 9.1) to be more similar to the reactivity of an epoxide or to the reactivity of a noncyclic ether?

9.9 USING CARBOCATION STABILITY TO DETERMINE THE CARCINOGENICITY OF AN ARENE OXIDE

An **arene oxide** is a compound in which one of the "double bonds" of an aromatic hydrocarbon (also called an **arene**) has been converted into an epoxide. Formation of an arene oxide is the first step in changing an aromatic compound that enters the body as a foreign substance (for example, a drug, cigarette smoke, automobile exhaust) into a more water-soluble compound that can eventually be eliminated. The enzyme that converts arenes into arene oxides is called cytochrome P_{450}.

benzene

benzene oxide

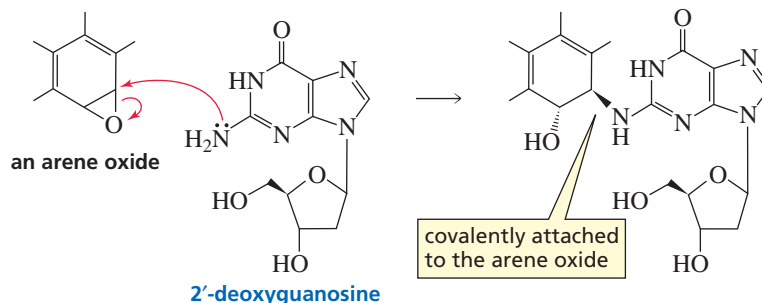
An arene oxide can react in two ways. It can react as a typical epoxide, undergoing attack by a nucleophile (Y^-) to form addition products (Section 9.8). Two addition products are obtained because the nucleophile can attack either of the carbons of the three-membered ring. Alternatively, it can rearrange to form a phenol, which other epoxides cannot do.

When an arene oxide undergoes rearrangement, the three-membered epoxide ring opens, picking up a proton from a species in the solution (HB^+). A base in the solution (:B) removes a proton from the carbocation intermediate; the product is phenol.

benzene oxide ⇌ a carbocation ⟶ phenol + HB^+

Because formation of the carbocation is the rate-determining step, the rate of phenol formation depends on the stability of the carbocation. The more stable the carbocation, the more easily the ring opens to form the rearranged product.

Some aromatic hydrocarbons are carcinogens—that is, compounds that cause cancer. Investigation has revealed, however, that the hydrocarbons themselves are not carcinogenic; the actual carcinogens are the arene oxides into which the hydrocarbons are converted in the body.

How do arene oxides cause cancer? We have seen that nucleophiles react with epoxides to form addition products. A nucleophilic NH_2 group of 2´-deoxyguanosine, a component of DNA (Section 21.1), is known to react with certain arene oxides. Once a molecule of 2´-deoxyguanosine becomes covalently attached to an arene oxide, the 2´-deoxyguanosine can no longer fit into the DNA double helix. As a result, the genetic code will not be properly transcribed (Section 21.7), which can lead to mutations that cause cancer. Cancer results when cells lose their ability to control their growth and reproduction.

A segment of DNA

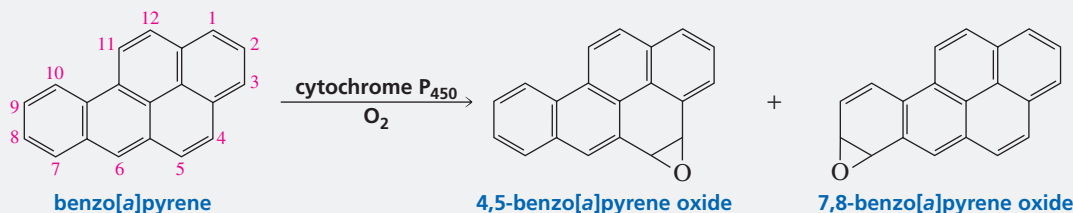
an arene oxide + 2′-deoxyguanosine ⟶ (covalently attached to the arene oxide)

Not all arene oxides are carcinogenic. Whether a particular arene oxide is carcinogenic depends on the relative rates of its two reaction pathways: rearrangement and reaction with a nucleophile. Arene oxide rearrangement leads to phenols that are not carcinogenic, whereas formation of addition products from nucleophilic attack by DNA can lead to cancer-causing products. Thus, if the rate of arene oxide rearrangement is faster than the rate of nucleophilic attack by DNA, then the arene oxide will be harmless. However, if the rate of nucleophilic attack is faster than the rate of rearrangement, the arene oxide will likely be a carcinogen.

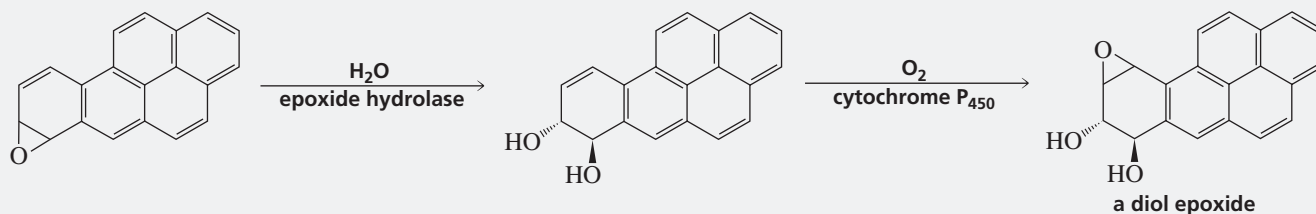
The more stable the carbocation formed when the arene oxide opens, the less likely it is that the arene oxide is carcinogenic.

We have seen that the rate-limiting step of arene oxide rearrangement is formation of the carbocation. Thus, the rate of the rearrangement reaction and an arene oxide's cancer-causing potential depend on the stability of the carbocation. If the carbocation is relatively stable, then it will be formed relatively easily, so rearrangement will be fast and the arene oxide will most likely not be carcinogenic. On the other hand, if the carbocation is relatively unstable, then rearrangement will be slow and the arene oxide will more likely exist long enough to be attacked by nucleophiles, and thus be carcinogenic. This means that *the more stable the carbocation formed when the epoxide ring of an arene oxide opens, the less likely it is that the arene oxide is carcinogenic.*

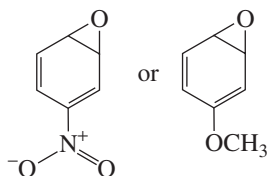
Benzo[*a*]pyrene and Cancer

Benzo[*a*]pyrene is one of the most carcinogenic arenes. It is formed whenever an organic compound is not completely burned. For example, benzo[*a*]pyrene is found in cigarette smoke, automobile exhaust, and charcoal-broiled meat. Several arene oxides can be formed from benzo[*a*]pyrene. The two most harmful are the 4,5-oxide and the 7,8-oxide.

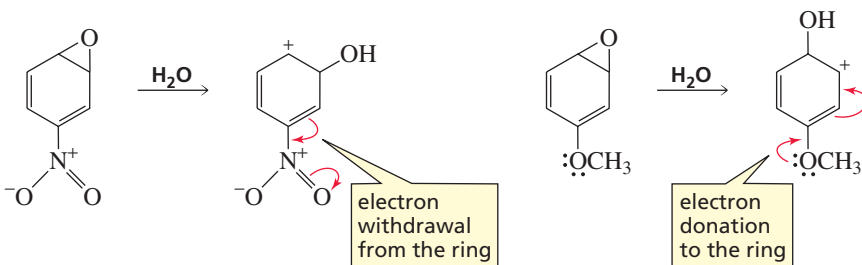
benzo[*a*]pyrene —cytochrome P_{450}, O_2→ 4,5-benzo[*a*]pyrene oxide + 7,8-benzo[*a*]pyrene oxide

The 4,5-oxide is harmful because it forms a carbocation that cannot be stabilized by electron delocalization without destroying the aromaticity of an adjacent benzene ring. Thus, the carbocation is relatively unstable, so the epoxide tends not to open until it is attacked by a nucleophile (the carcinogenic pathway). The 7,8-oxide is harmful because it reacts with water (a nucleophile) to form a diol, which then forms a diol epoxide. The diol epoxide does not readily undergo rearrangement (the harmless pathway), because it opens to a carbocation that is destabilized by the electron-withdrawing OH groups. Since carbocation formation is slow, the diol epoxide can exist long enough to be attacked by nucleophiles.

7,8-oxide —H_2O, epoxide hydrolase→ diol —O_2, cytochrome P_{450}→ a diol epoxide

PROBLEM 22 Solved

Which compound is more likely to be carcinogenic?

(nitro-substituted arene oxide) or (methoxy-substituted arene oxide, OCH_3)

Solution The nitro-substituted compound is more likely to be carcinogenic. The nitro group destabilizes the carbocation formed when the ring opens by withdrawing electrons from the ring by resonance. In contrast, the methoxy group stabilizes the carbocation by donating electrons to the ring by resonance (Section 7.9). Carbocation formation leads to the harmless product, so the nitro-substituted compound with a less stable (less easily formed) carbocation will be less likely to undergo rearrangement to a harmless product. In addition, the electron-withdrawing nitro group increases the arene oxide's susceptibility to nucleophilic attack, which is the cancer-causing pathway.

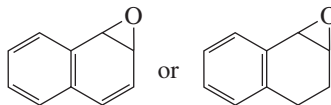
H_2O → electron withdrawal from the ring

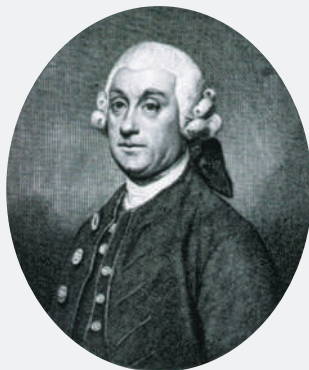
H_2O → electron donation to the ring

PROBLEM 23

Explain why the two arene oxides in Problem 22 open in opposite directions.

PROBLEM 24♦

Which compound is more likely to be carcinogenic? (*Hint:* Read the box on benzo[*a*]pyrene to see why the 4,5-epoxide is harmful.)

[naphthalene 1,2-epoxide] or [tetrahydronaphthalene 1,2-epoxide]

Chimney Sweeps and Cancer

In 1775, British physician Percival Pott became the first to recognize that environmental factors can cause cancer when he observed that chimney sweeps had a higher incidence of scrotum cancer than the male population as a whole. He theorized that something in the chimney soot was causing cancer. We now know that it was benzo[*a*]pyrene.

Percival Pott

A Victorian chimney sweep and his assistant—a boy small enough to fit inside narrow passages.

9.10 AMINES DO NOT UNDERGO SUBSTITUTION OR ELIMINATION REACTIONS

Although **amines,** like alkyl halides, alcohols, and ethers, have an electron-withdrawing group bonded to an sp^3 carbon, amines do not undergo substitution and elimination reactions.

An amine's lack of reactivity in substitution and elimination reactions can be understood by comparing the leaving propensity of its electron-withdrawing group with the leaving propensity of the electron-withdrawing groups of the compounds that do undergo substitution and/or elimination reactions.

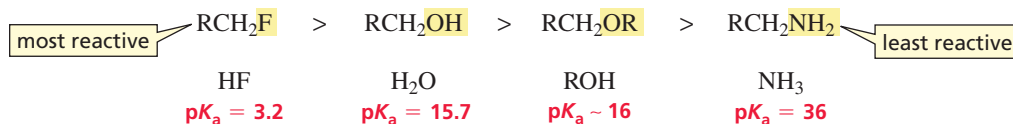
The relative leaving propensities of the groups can be determined by comparing the pK_a values of their conjugate acids, recalling that the weaker the acid, the stronger its conjugate base and the poorer the base is as a leaving group. The pK_a values of the conjugate acids show that the leaving group of an amine ($^-NH_2$) is such a strong base that amines cannot undergo substitution or elimination reactions. (HF has been used for the comparison since F is in the same row of the periodic chart as O and N, but recall that an alkyl fluoride has the poorest leaving group of the alkyl halides.)

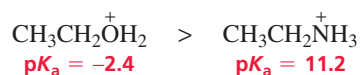
The weaker the acid, the stronger its conjugate base.

The stronger the base, the poorer it is as a leaving group.

relative reactivities

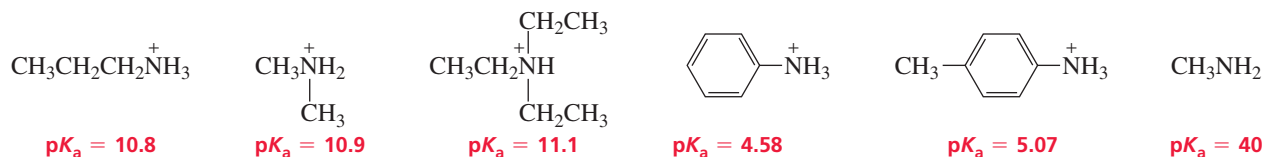
most reactive RCH_2F > RCH_2OH > RCH_2OR > RCH_2NH_2 least reactive

HF	H_2O	ROH	NH_3
$pK_a = 3.2$	$pK_a = 15.7$	$pK_a \sim 16$	$pK_a = 36$

Protonating the amino group makes it a better leaving group, but not nearly as good as a protonated alcohol, which is almost 14 pK_a units more acidic than a protonated amine.

$$\underset{pK_a = -2.4}{CH_3CH_2\overset{+}{O}H_2} > \underset{pK_a = 11.2}{CH_3CH_2\overset{+}{N}H_3}$$

Therefore, unlike protonated alcohols, protonated amines cannot undergo substitution and elimination reactions.

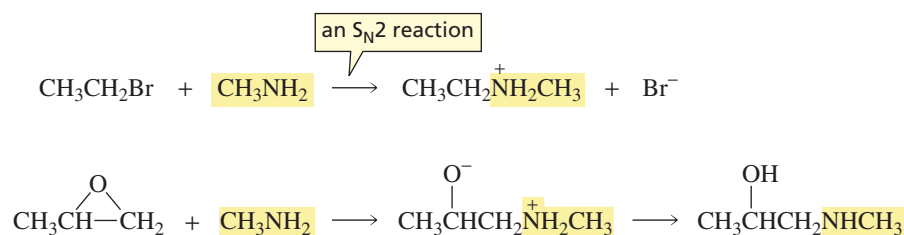
Although they cannot undergo substitution or elimination reactions, amines are extremely important organic compounds. The lone pair on its nitrogen allows an amine to react both as a base and as a nucleophile.

Amines are the most common organic bases. We have seen that protonated amines have pK_a values of about 11 and that protonated anilines have pK_a values of about 5 (Sections 2.3 and 7.8). Neutral amines have very high pK_a values. For example, the pK_a of methylamine is 40.

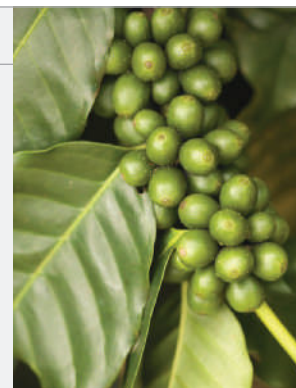
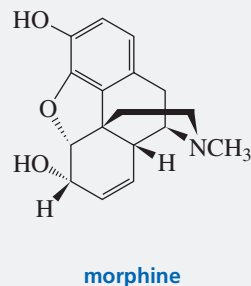
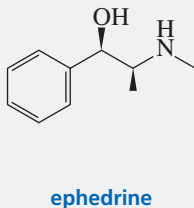
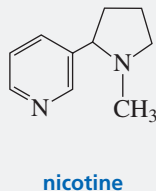
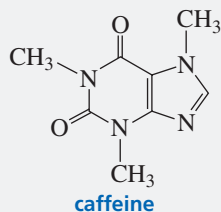
$CH_3CH_2CH_2\overset{+}{N}H_3$	$CH_3\overset{+}{N}H_2CH_3$	$CH_3CH_2\overset{+}{N}H(CH_2CH_3)_2$	$C_6H_5\overset{+}{N}H_3$	$CH_3C_6H_4\overset{+}{N}H_3$	CH_3NH_2
pK_a = 10.8	pK_a = 10.9	pK_a = 11.1	pK_a = 4.58	pK_a = 5.07	pK_a = 40

Amines react as nucleophiles in a wide variety of reactions. For example, we have seen that they react as nucleophiles with alkyl halides and epoxides in S_N2 reactions.

an S_N2 reaction

$$CH_3CH_2Br + CH_3NH_2 \longrightarrow CH_3CH_2\overset{+}{N}H_2CH_3 + Br^-$$

$$CH_3\underset{\text{epoxide}}{CH{-}CH_2} + CH_3NH_2 \longrightarrow CH_3CH(O^-)CH_2\overset{+}{N}H_2CH_3 \longrightarrow CH_3CH(OH)CH_2NHCH_3$$

In Chapters 11 and 12, we will see that amines also react as nucleophiles with a wide variety of carbonyl compounds.

Alkaloids

Alkaloids are amines found in the leaves, bark, roots, or seeds of many plants. Examples include caffeine (found in tea leaves, coffee beans, and cola nuts) and nicotine (found in tobacco leaves). Nicotine causes brain cells to release dopamine and endorphins, compounds that makes us feel good, thereby making nicotine addictive. Ephedrine, a bronchodilator, is an alkaloid obtained from *Ephedra sinica*, a plant found in China. Morphine is an alkaloid obtained from opium, a milky fluid exuded by a species of poppy (page 30).

coffee beans

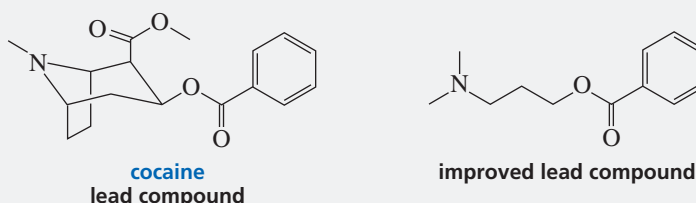
Lead Compounds for the Development of Drugs

Medicinal agents used by humans since ancient times provided the starting point for the development of our current arsenal of drugs. The active ingredients were isolated from the herbs, berries, roots, and bark used by medicine men and women, shamans, and witch doctors. Scientists still search the world for plants, berries, flora, and fauna that might yield new medicinal compounds.

Once a naturally occurring drug is isolated and its structure determined, it can serve as a prototype in a search for other biologically active compounds. The prototype is called a **lead compound** (that is, it plays a leading role in the search). Analogues of the lead compound are synthesized and tested to see if they are more effective or have fewer side effects than the lead compound. An analogue may have a different substituent than the lead compound, a branched chain instead of a straight chain, a different functional group, or some other structural difference. Producing analogues by changing the structure of a lead compound is called **molecular modification.**

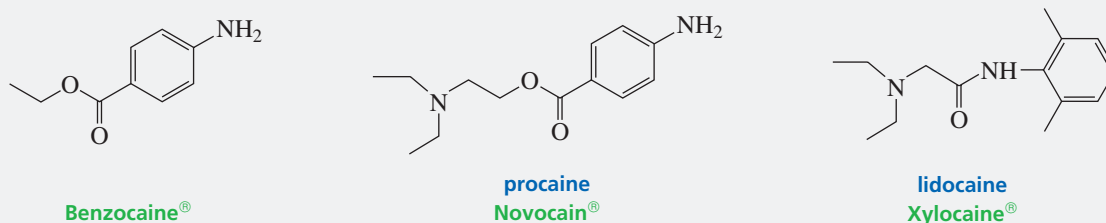
In a classic example of molecular modification, a number of synthetic local anesthetics were developed from cocaine, an alkaloid obtained from the leaves of *Erythroxylon coca*, a bush native to the highlands of the South American Andes (see page 331). Cocaine is a highly effective local anesthetic, but it produces undesirable effects on the central nervous system (CNS), ranging from initial euphoria to severe depression. By dissecting the cocaine molecule step by step—removing the methoxycarbonyl group and cleaving the seven-membered-ring system—scientists identified the portion of the molecule that carries the local anesthetic activity but does not induce the damaging CNS effects. This knowledge provided an improved lead compound.

cocaine
lead compound

improved lead compound

Hundreds of analogues were then synthesized. Successful anesthetics obtained by molecular modification were Benzocaine (a topical anesthetic), Novocain (used by dentists), and Xylocaine (one of the most widely used injectable anesthetics).

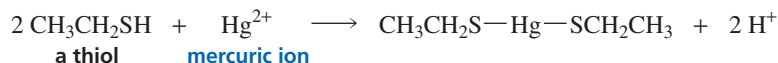
Benzocaine®

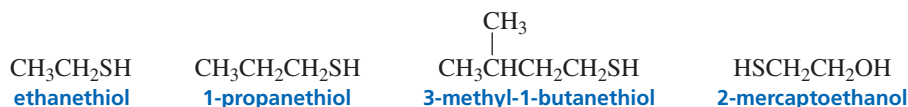
procaine
Novocain®

lidocaine
Xylocaine®

9.11 THIOLS, SULFIDES, AND SULFONIUM SALTS

Thiols are sulfur analogues of alcohols. They used to be called mercaptans because they form strong complexes with heavy metal cations such as arsenic and mercury—that is, they capture mercury.

$$2\ CH_3CH_2SH + Hg^{2+} \longrightarrow CH_3CH_2S{-}Hg{-}SCH_2CH_3 + 2\ H^+$$

a thiol — mercuric ion

Thiols are named by adding the suffix *thiol* to the name of the parent hydrocarbon. If there is a second functional group in the molecule that is identified by a suffix, the SH group can be indicated by its substituent name, *mercapto*. Like other substituent names, it is placed before the name of the parent hydrocarbon.

CH_3CH_2SH	$CH_3CH_2CH_2SH$	$CH_3CH(CH_3)CH_2CH_2SH$	$HSCH_2CH_2OH$
ethanethiol	1-propanethiol	3-methyl-1-butanethiol	2-mercaptoethanol

Because sulfur is not as electronegative as oxygen, thiols are not good at hydrogen bonding. Consequently, they have weaker intermolecular attractions and, therefore, considerably lower boiling points than alcohols (Section 3.7). For example, the boiling point of CH_3CH_2SH is 37 °C, whereas the boiling point of CH_3CH_2OH is 78 °C.

Sulfur atoms are larger than oxygen atoms, so the negative charge of the thiolate ion is spread over a larger volume of space than the negative charge of an alkoxide ion, causing the thiolate ion to be more stable (Section 2.6). Thiols, therefore, are stronger acids (pK_a ~10) than alcohols (pK_a ~15). Even though a thiolate ion is a weaker base than an alkoxide ion, the larger thiolate ion is less well solvated, so it is a better nucleophile (Section 8.12).

$$CH_3{-}\ddot{\underset{..}{S}}{:}^- + CH_3CH_2{-}Br \xrightarrow{CH_3OH} CH_3{-}\ddot{\underset{..}{S}}{-}CH_2CH_3 + Br^-$$

Low-molecular-weight thiols are noted for their strong and pungent odors, such as the odors associated with onions, garlic, and skunks. Natural gas is completely odorless and can cause deadly explosions if a leak goes undetected. As a result, a small amount of a thiol is added to natural gas to give it an odor so that gas leaks can be detected.

The sulfur analogues of ethers are called **sulfides** or **thioethers.** Sulfides react readily with alkyl halides to form **sulfonium salts,** whereas ethers do not react with alkyl halides because oxygen is not as nucleophilic as sulfur and cannot accommodate a positive charge as well as sulfur can.

$$CH_3{-}\ddot{\underset{..}{S}}{-}CH_3 + CH_3{-}I \longrightarrow CH_3{-}\overset{+}{\underset{..}{S}}(CH_3){-}CH_3 \;\; I^-$$

dimethyl sulfide
a thioether

trimethylsulfonium iodide
a sulfonium salt

The positively charged group of a **sulfonium ion** is an excellent leaving group, so a sulfonium ion readily undergoes nucleophilic substitution reactions.

$$H\ddot{\underset{..}{O}}{:}^- + CH_3{-}\overset{+}{\underset{..}{S}}(CH_3){-}CH_3 \longrightarrow CH_3{-}\ddot{\underset{..}{O}}H + CH_3{-}\ddot{\underset{..}{S}}{-}CH_3$$

a sulfonium ion

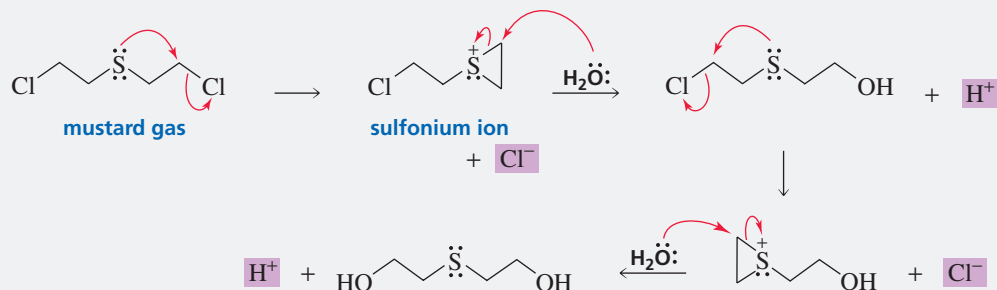
Mustard Gas—A Chemical Warfare Agent

Chemical warfare occurred for the first time in 1915, when Germany released chlorine gas against French and British forces in the Battle of Ypres. For the remainder of World War I, both sides used a variety of chemical agents as weapons. One of the more common was mustard gas, a reagent that produces large blisters on exposed skin. Mustard gas is extremely reactive because its highly nucleophilic sulfur atom easily displaces a chloride ion by an intramolecular S_N2 reaction, forming a cyclic sulfonium ion that reacts rapidly with a nucleophile. The sulfonium ion is particularly reactive because of its strained three-membered ring and its excellent (positively charged) leaving group.

$$ClCH_2CH_2\ddot{S}CH_2CH_2Cl \longrightarrow \text{sulfonium ion} + Cl^- \xrightarrow{H_2\ddot{O}:} ClCH_2CH_2\ddot{S}CH_2CH_2OH + H^+$$

mustard gas

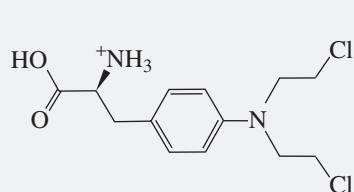
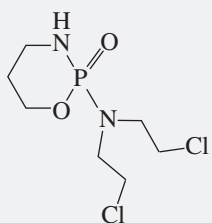
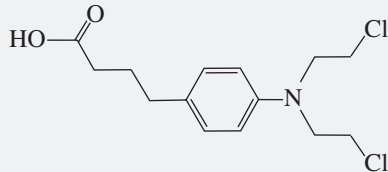
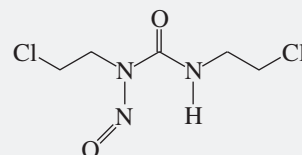
sulfonium ion

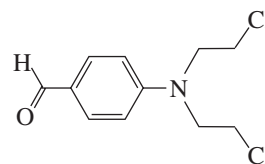
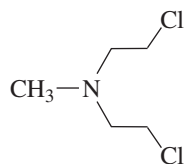
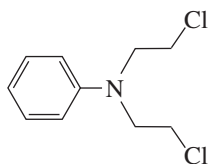
$$\longrightarrow \text{cyclic sulfonium ion} + Cl^- \xrightarrow{H_2\ddot{O}:} HOCH_2CH_2\ddot{S}CH_2CH_2OH + H^+$$

The blistering caused by mustard gas results from the high local concentrations of HCl produced when mustard gas comes into contact with water—or any other nucleophile—on skin or in lung tissue. Autopsies of soldiers killed by mustard gas in World War I revealed that they had extremely low white blood cell counts and defects in bone marrow development, indicating profound effects on rapidly dividing cells.

Alkylating Agents as Cancer Drugs

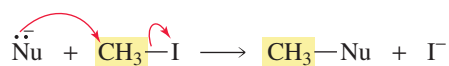
Since cancer is characterized by the uncontrolled growth and proliferation of cells, the discovery that mustard gas affected rapidly dividing cells suggested that it might be an effective antitumor agent. Therefore, chemists started looking for less reactive analogues of mustard gas that might be used in chemotherapy—that is, the use of chemicals in the treatment of cancer.

Because mustard gas forms a three-membered ring that can react rapidly with nucleophiles, its clinical reactivity is thought to be due to its ability to alkylate groups on the surface of DNA. Alkylating DNA can destroy it, which means that the rapidly growing cells of cancerous tumors are killed. Unfortunately, compounds used for chemotherapy can also kill normal cells. That is why many side effects, such as nausea and hair loss, are associated with cancer chemotherapy. The challenge for chemists now is to find drugs that will target only cancer cells.

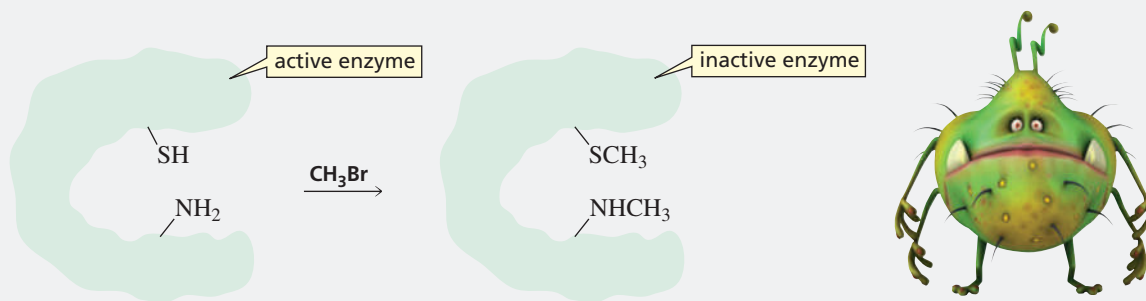
The cancer drugs shown here are all biological alkylating agents—they attach an alkyl group to a nucleophile under physiological conditions.

melphalan cyclophosphamide chloroambucil carmustine

PROBLEM 25♦

The following three nitrogen mustards were studied for possible clinical use. One is now used clinically, one was found to be too unreactive, and one was found to be too insoluble in water to be injected intravenously. Which is which? (*Hint:* Draw resonance contributors.)

9.12 METHYLATING AGENTS USED BY CHEMISTS VERSUS THOSE USED BY CELLS

If an organic chemist wanted to put a methyl group on a nucleophile, methyl iodide would most likely be used as the methylating agent. Of the methyl halides, methyl iodide has the most easily displaced leaving group because I^- is the weakest base of the halide ions. The reaction would be a simple S_N2 reaction.

$$\ddot{N}u^- + CH_3{-}I \longrightarrow CH_3{-}Nu + I^-$$

Methyl halides, however, are not available in cells. Because alkyl halides are only slightly soluble in water, they are not found in the predominantly aqueous environments of biological systems. Instead, cells use *S*-adenosylmethionine (SAM; also called AdoMet), a water-soluble compound, as a methylating agent. (A less common biological methylating agent is discussed in Section 18.13.)

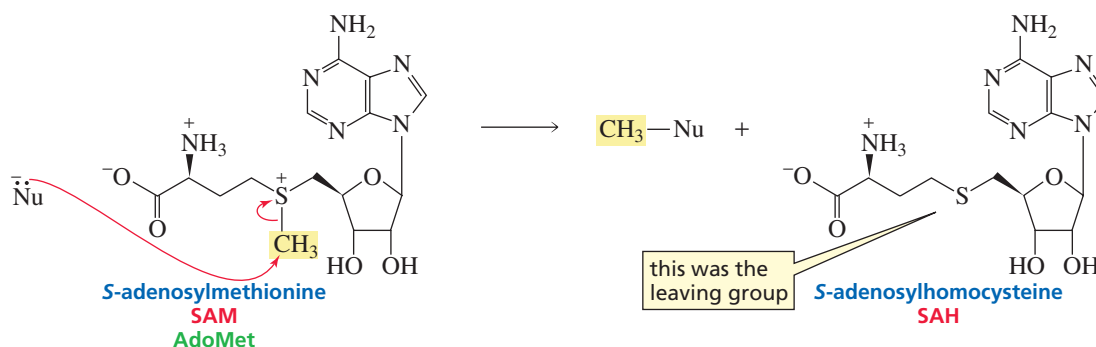
Eradicating Termites

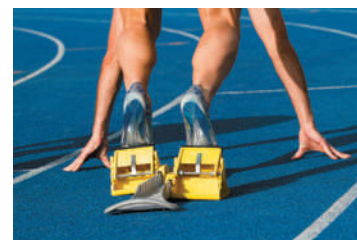
Alkyl halides can be very toxic to biological organisms. For example, bromomethane is used to kill termites and other pests. Bromomethane works by methylating the NH_2 and SH groups of enzymes, thereby destroying the enzymes' ability to catalyze biological reactions. Unfortunately, bromomethane has been found to deplete the ozone layer (Section 14.8), so its production has recently been banned in developed countries; developing countries must ban its use by 2015.

Although SAM is a much larger and more complicated-looking molecule than methyl iodide, it performs the same function—namely, it transfers a methyl group to a nucleophile. Remember that biological molecules are typically more complex than the molecules chemists use because of the need for molecular recognition (Section 5.11).

S-adenosylmethionine
SAM
AdoMet

CH_3—Nu +

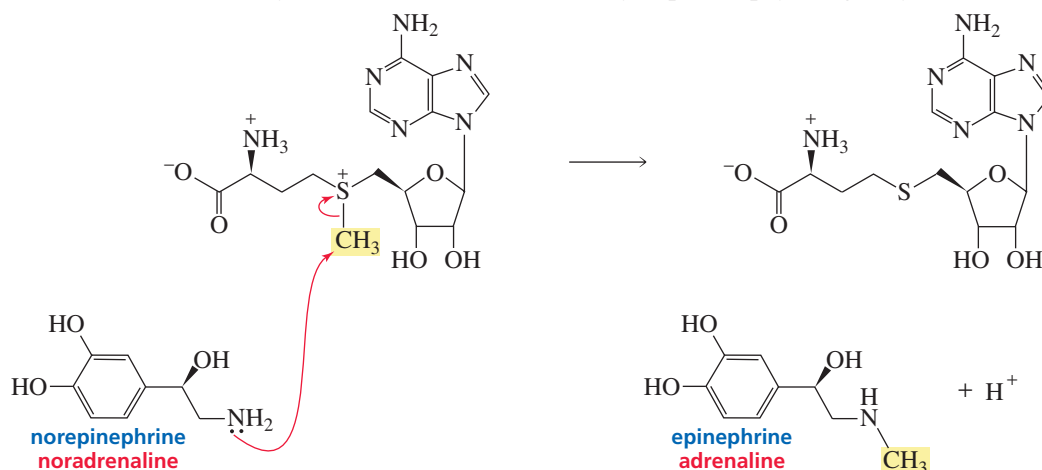
this was the leaving group

S-adenosylhomocysteine
SAH

Notice that the methyl group of SAM is attached to a positively charged sulfur, which can readily accept the electrons left behind when the methyl group is transferred. In other words, the methyl group is attached to a very good leaving group, allowing biological methylation to take place at a reasonable rate.

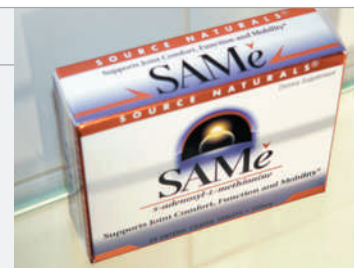
A specific example of a biological methylation reaction that uses SAM is the conversion of noradrenaline (norepinephrine) to adrenaline (epinephrine). The reaction uses SAM to provide the methyl group. Noradrenaline and adrenaline are hormones that stimulate the breakdown of glycogen—the body's primary fuel source. You may have felt this "adrenaline rush" when preparing for a challenging activity. Adrenaline is about six times more potent than noradrenaline. This methylation reaction, therefore, is very important physiologically.

experiencing an adrenaline rush

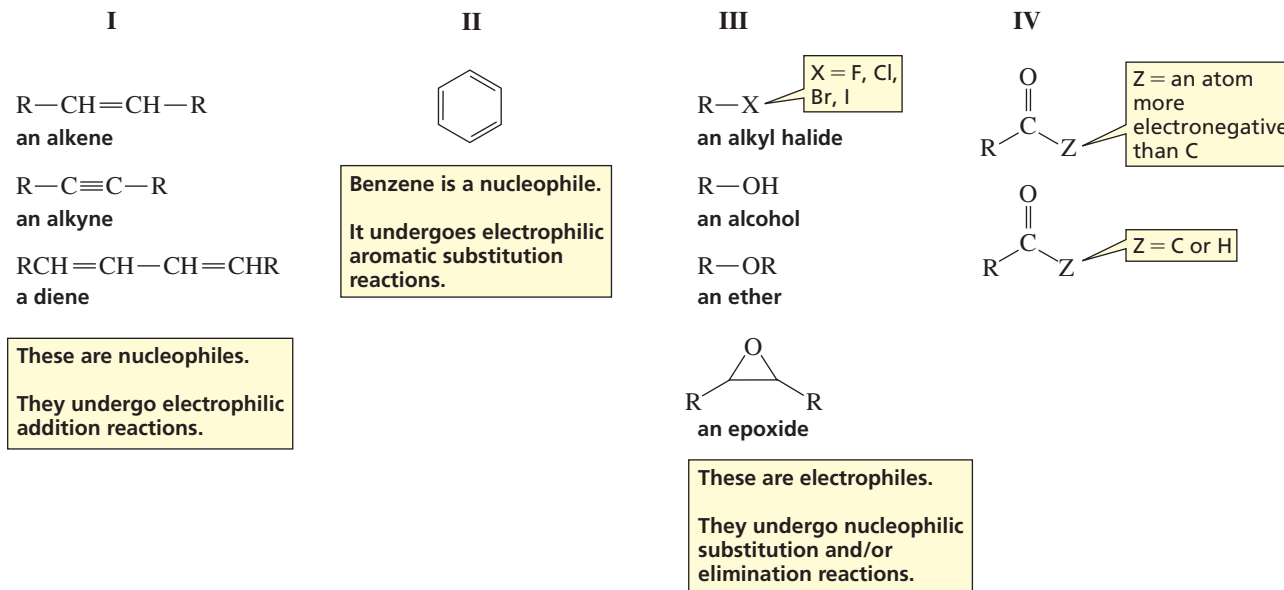
norepinephrine
noradrenaline

epinephrine
adrenaline

+ H^+

S-Adenosylmethionine: A Natural Antidepressant

Marketed under the name SAMe (pronounced Sammy), *S*-adenosylmethionine is sold in many health food and drug stores as a treatment for depression and arthritis. Although SAMe has been used clinically in Europe for more than two decades, it has not been rigorously evaluated in the United States and therefore has not been approved by the FDA. It can be sold, however, because the FDA does not prohibit the sale of most naturally occurring substances as long as the marketer does not make therapeutic claims.

SAMe has also been found to be effective in the treatment of liver diseases, such as those caused by alcohol and the hepatitis C virus. The attenuation of injury to the liver is accompanied by an increase in the concentration of glutathione in the liver. Glutathione is an important biological antioxidant (Section 17.8). SAM is required for the biosynthesis of cysteine, one of the 20 most common naturally occurring amino acids (Section 17.1), which is required for the biosynthesis of glutathione.

9.13 ORGANIZING WHAT WE KNOW ABOUT THE REACTIONS OF ORGANIC COMPOUNDS

We have seen that the families of organic compounds can be put into one of four groups, and that all the members of a group react in similar ways. Now that we have finished studying the families in Group III, let's revisit it.

All the families in Group III are *electrophiles*, due to the partial positive charge on the carbon attached to the electron-withdrawing leaving group. As a result, the families in this group react with *nucleophiles*. The nucleophile can either attack the carbon to which the electron-withdrawing group is attached and substitute for it, or it can remove a hydrogen from an adjacent carbon and eliminate the electron-withdrawing group by forming an alkene. Thus, the families in Group III undergo nucleophilic substitution reactions and/or elimination reactions.

- Alkyl halides have excellent leaving groups, so they undergo substitution and/or elimination reactions with ease.
- Alcohols and ethers have much poorer leaving groups, so they have to be activated before they can undergo nucleophilic substitution and/or elimination reactions.
- Epoxides are more reactive than noncyclic ethers because of the angle strain in the three-membered ring. Thus, they readily undergo substitution reactions whether or not they are activated by protonation.

SOME IMPORTANT THINGS TO REMEMBER

- The leaving groups of **alcohols** and **ethers** are stronger bases than halide ions, so alcohols and ethers have to be "activated" before they can undergo a substitution or an elimination reaction.
- Alcohols and ethers can be activated by protonation.
- Cells use ATP to activate alcohols.
- **Epoxides** do not have to be activated, because ring strain increases their reactivity.
- Primary, secondary, and tertiary alcohols undergo nucleophilic substitution reactions with HI, HBr, and HCl to form alkyl halides. These are S_N1 reactions in the case of secondary and tertiary alcohols and S_N2 reactions in the case of primary alcohols.
- An alcohol undergoes **dehydration** (elimination of a water molecule) when it is heated with an acid.
- Dehydration is an E1 reaction in the case of secondary and tertiary alcohols and an E2 reaction in the case of primary alcohols.
- Tertiary alcohols are the easiest to dehydrate, and primary alcohols are the hardest.
- The major product of alcohol dehydration is the more stable alkene.
- If the alkene has stereoisomers, the stereoisomer in which the largest groups are on opposite sides of the double bond will be the major product.
- Chromic acid oxidizes primary alcohols to carboxylic acids and secondary alcohols to ketones.
- Hypochlorous acid oxidizes primary alcohols to aldehydes and secondary alcohols to ketones.
- Ethers can undergo nucleophilic substitution reactions with HBr or HI and heat. If departure of the leaving group creates a relatively stable carbocation, an S_N1 reaction occurs; otherwise, an S_N2 reaction occurs.
- **Epoxides** undergo nucleophilic substitution reactions. Under acidic conditions, the more substituted ring carbon is attacked; under neutral or basic conditions, the less sterically hindered ring carbon is attacked.
- Aromatic hydrocarbons (**arenes**) are oxidized to **arene oxides** that undergo rearrangement to form phenols, or undergo nucleophilic attack to form addition products.
- The more stable the carbocation formed during rearrangement, the less likely it is that the arene oxide is carcinogenic.
- Amines cannot undergo substitution or elimination reactions because their leaving groups are very strong bases.
- **Thiols** are sulfur analogues of alcohols. They are stronger acids than alcohols and have lower boiling points.
- Thiolate ions are weaker bases and better nucleophiles than alkoxide ions.
- **Thioethers** react with alkyl halides to form **sulfonium ions**, which have excellent leaving groups, so they undergo substitution reactions with ease.

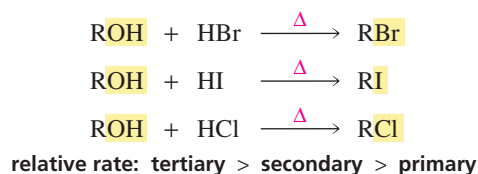
SUMMARY OF REACTIONS

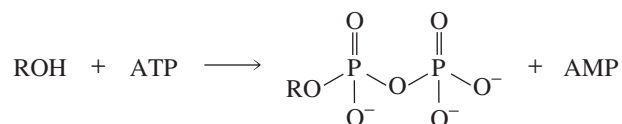
1. Converting an *alcohol* into an *alkyl halide* (Section 9.2). The mechanisms are shown on page 335.

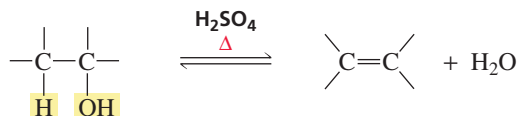
$$\text{ROH} + \text{HBr} \xrightarrow{\Delta} \text{RBr}$$

$$\text{ROH} + \text{HI} \xrightarrow{\Delta} \text{RI}$$

$$\text{ROH} + \text{HCl} \xrightarrow{\Delta} \text{RCl}$$

relative rate: tertiary > secondary > primary

2. Cells activate alcohols by reacting with ATP (Section 9.3). The mechanism is shown on page 337.

$$\text{ROH} + \text{ATP} \longrightarrow \text{RO}-\overset{\overset{\text{O}}{\|}}{\underset{\underset{\text{O}^-}{|}}{\text{P}}}-\text{O}-\overset{\overset{\text{O}}{\|}}{\underset{\underset{\text{O}^-}{|}}{\text{P}}}-\text{O}^- + \text{AMP}$$

3. Elimination reactions of alcohols: dehydration (Section 9.4). The mechanisms are shown on pages 339 and 340.

$$-\overset{|}{\underset{\underset{H}{|}}{C}}-\overset{|}{\underset{\underset{OH}{|}}{C}}- \underset{}{\overset{H_2SO_4,\ \Delta}{\rightleftharpoons}} \;\rangle C{=}C\langle \; + \; H_2O$$

relative rate: tertiary > secondary > primary

4. Oxidation of alcohols (Section 9.5). The mechanism for oxidation by HOCl is shown on page 342.

primary alcohols $RCH_2OH \xrightarrow{H_2CrO_4} \left[R-\overset{O}{\overset{\|}{C}}-H \right] \xrightarrow[\text{oxidation}]{\text{further}} R-\overset{O}{\overset{\|}{C}}-OH$

a carboxylic acid

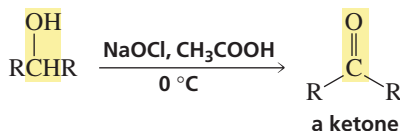
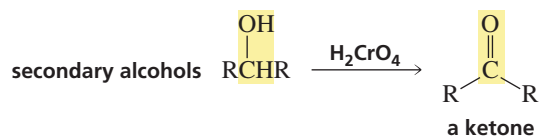
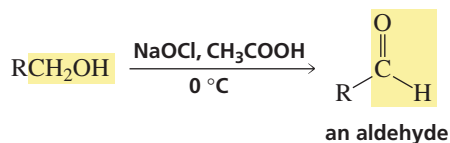
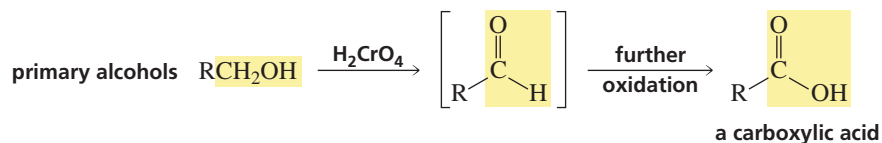
$RCH_2OH \xrightarrow[0\ °C]{NaOCl,\ CH_3COOH} R-\overset{O}{\overset{\|}{C}}-H$

an aldehyde

secondary alcohols $R\overset{OH}{\overset{|}{C}}HR \xrightarrow{H_2CrO_4} R-\overset{O}{\overset{\|}{C}}-R$

a ketone

$R\overset{OH}{\overset{|}{C}}HR \xrightarrow[0\ °C]{NaOCl,\ CH_3COOH} R-\overset{O}{\overset{\|}{C}}-R$

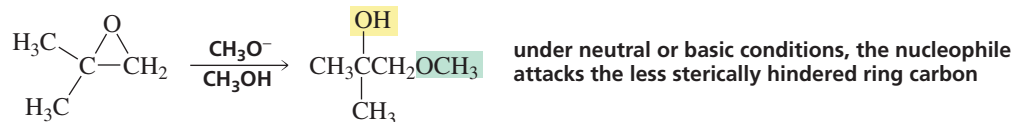
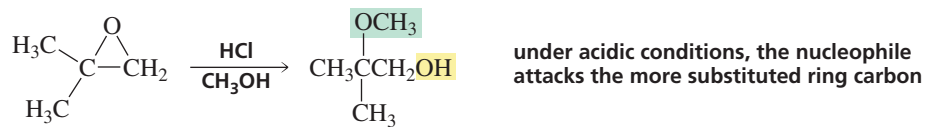
a ketone

5. Nucleophilic substitution reactions of ethers (Section 9.7). The mechanisms are shown on pages 345 and 346.

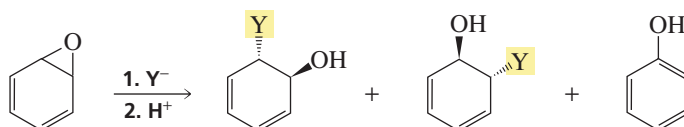
$$ROR' + HX \xrightarrow{\Delta} ROH + R'X$$

HX = HBr or HI

6. Nucleophilic substitution reactions of *epoxides* (Section 9.8). The mechanisms are shown on pages 348 and 350.

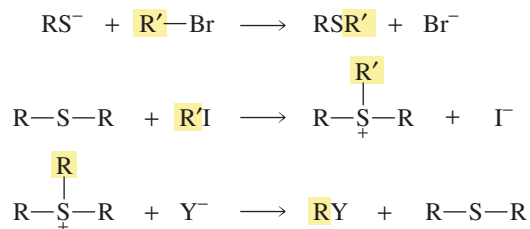
$(H_3C)_2\overset{O}{C{-}CH_2} \xrightarrow[CH_3OH]{HCl} CH_3\overset{OCH_3}{\underset{CH_3}{C}}CH_2OH$ **under acidic conditions, the nucleophile attacks the more substituted ring carbon**

$(H_3C)_2\overset{O}{C{-}CH_2} \xrightarrow[CH_3OH]{CH_3O^-} CH_3\overset{OH}{\underset{CH_3}{C}}CH_2OCH_3$ **under neutral or basic conditions, the nucleophile attacks the less sterically hindered ring carbon**

7. Reactions of *arene oxides:* ring opening and rearrangement (Section 9.9). The mechanisms are shown on page 352.

arene oxide $\xrightarrow[\text{2. } H^+]{\text{1. } Y^-}$ trans-Y,OH cyclohexadiene + trans-OH,Y cyclohexadiene + phenol (OH)

8. Reactions of thiols, sulfides, and sulfonium ions (Section 9.11). The mechanisms are shown on pages 356 and 357.

$$RS^- + R'{-}Br \longrightarrow RSR' + Br^-$$

$$R{-}S{-}R + R'I \longrightarrow R{-}\overset{R'}{\underset{+}{S}}{-}R + I^-$$

$$R{-}\overset{R}{\underset{+}{S}}{-}R + Y^- \longrightarrow RY + R{-}S{-}R$$

PROBLEMS

26. Give the product of each of the following reactions:

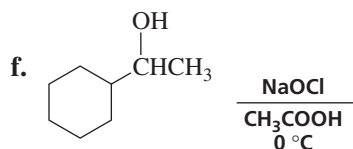
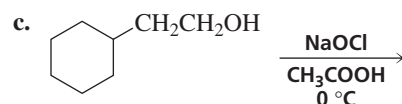
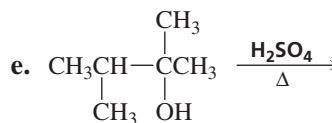
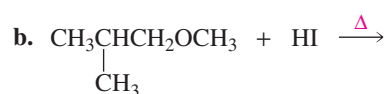
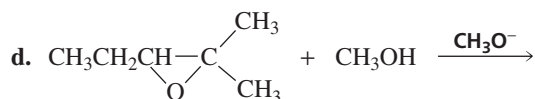
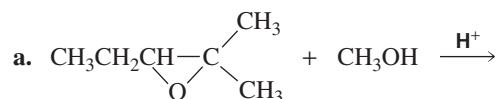
a. $CH_3CH_2CH{-}C(CH_3)_2$ (epoxide, O bridging CH and C) $+ CH_3OH \xrightarrow{H^+}$

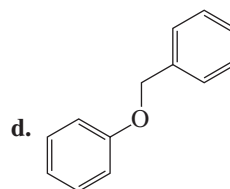
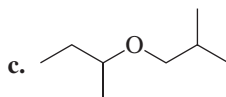
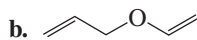
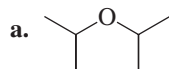
b. $CH_3CH(CH_3)CH_2OCH_3 + HI \xrightarrow{\Delta}$

c. cyclohexyl–$CH_2CH_2OH \xrightarrow[CH_3COOH,\ 0\ °C]{NaOCl}$

d. $CH_3CH_2CH{-}C(CH_3)_2$ (epoxide, O bridging CH and C) $+ CH_3OH \xrightarrow{CH_3O^-}$

e. $CH_3CH(CH_3){-}C(CH_3)(OH)CH_3 \xrightarrow[\Delta]{H_2SO_4}$

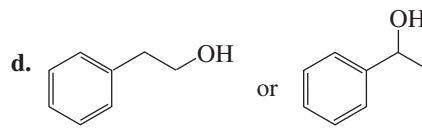
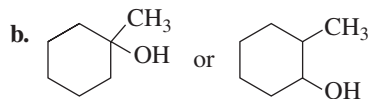
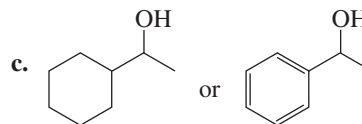
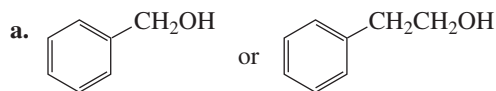
f. cyclohexyl–$CH(OH)CH_3 \xrightarrow[CH_3COOH,\ 0\ °C]{NaOCl}$

27. What are the common and systematic names of the following ethers?

a. O **b.** O **c.** O **d.** O

28. Indicate which alcohol in each pair will undergo an elimination reaction more rapidly when heated with H_2SO_4.

a. $C_6H_5CH_2OH$ or $C_6H_5CH_2CH_2OH$

b. 1-methylcyclohexanol (CH_3, OH) or 2-methylcyclohexanol (CH_3, OH)

c. OH (cyclohexyl) or OH (phenyl)

d. OH or OH

29. Name each of the following:

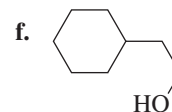
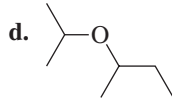
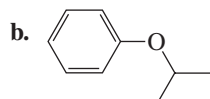
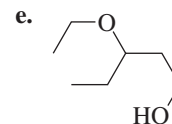
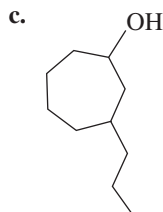
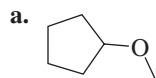
a. O

b. O

c. OH

d. O

e. O, HO

f. HO

30. Draw structures for the following:

a. isoproyl propyl ether **b.** butyl ethyl ether **c.** *sec*-butyl methyl ether **d.** diisopropyl ether

31. Draw the major product(s) of each of the following reactions:

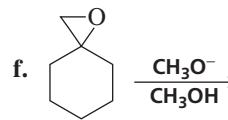
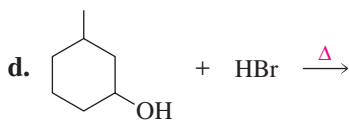
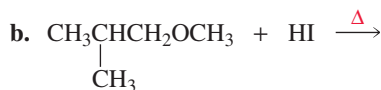
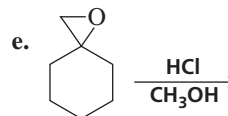
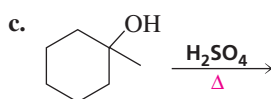
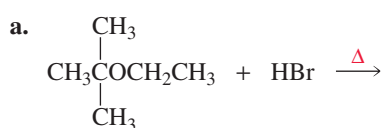
a. $CH_3C(CH_3)_2OCH_2CH_3 + HBr \xrightarrow{\Delta}$

b. $CH_3CH(CH_3)CH_2OCH_3 + HI \xrightarrow{\Delta}$

c. 1-methylcyclohexanol (OH) $\xrightarrow[\Delta]{H_2SO_4}$

d. 3-methylcyclohexanol (OH) $+ HBr \xrightarrow{\Delta}$

e. spiro-epoxide of cyclohexane (O) $\xrightarrow[CH_3OH]{HCl}$

f. spiro-epoxide of cyclohexane (O) $\xrightarrow[CH_3OH]{CH_3O^-}$

32. What is the major product obtained from the reaction of 2-propyloxirane with each of the following reagents?

a. 0.5 M HCl **b.** CH_3OH/HCl **c.** 0.1 M NaOH **d.** $CH_3CH_2OH/CH_3CH_2O^-$

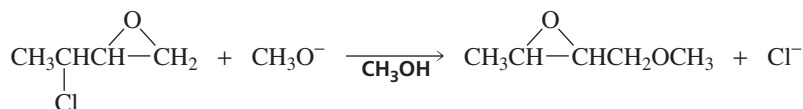
33. Draw structures for the following:

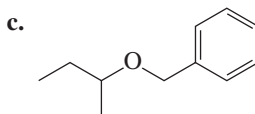
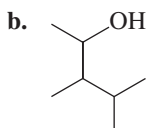
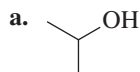
a. *cis*-3-ethylcyclohexanoll **b.** 2-ethoxy-1-propanol

34. Give the product formed from the reaction of each of the following compounds with HOCl:

a. 3-ethyl-2-decanol **b.** pentan-1-ol **c.** 2-propylcycloheptanol

35. Propose a mechanism for the following reaction:

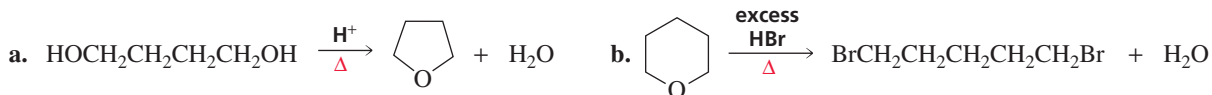
$$CH_3CH(Cl)CH\overset{O}{—}CH_2 + CH_3O^- \xrightarrow[CH_3OH]{} CH_3CH\overset{O}{—}CHCH_2OCH_3 + Cl^-$$

36. Name each of the following:

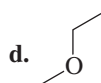
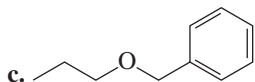
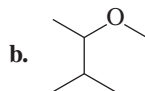
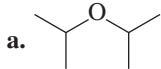
a. OH **b.** OH **c.** O

37. When ethyl ether is heated with excess HI for several hours, the only organic product obtained is ethyl iodide. Explain why ethyl alcohol is not obtained as a product.

38. Ethylene oxide reacts readily with HO^- because of the strain in the three-membered ring. Explain why cyclopropane, a compound with approximately the same amount of strain, does not react with HO^-.

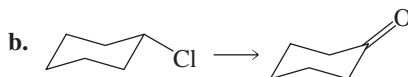
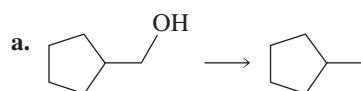
39. Propose a mechanism for each of the following reactions:

a. $HOCH_2CH_2CH_2CH_2OH \xrightarrow[\Delta]{H^+}$ tetrahydrofuran (O) $+ H_2O$

b. tetrahydropyran (O) $\xrightarrow[\Delta]{\text{excess HBr}} BrCH_2CH_2CH_2CH_2CH_2Br + H_2O$

40. Which of the following ethers would be obtained in greatest yield directly from alcohols?

a. O **b.** O **c.** O **d.** O

41. Show how each of the following syntheses could be carried out using the given starting material and any necessary reagents.

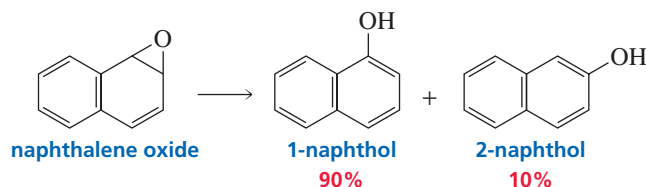
a. OH → (cyclopentylmethanol → methylcyclopentane)

b. Cl → O

42. Explain why (*S*)-2-butanol forms a racemic mixture when it is heated in sulfuric acid.

43. Triethylene glycol is one of the products obtained from the reaction of ethylene oxide and hydroxide ion. Propose a mechanism for its formation.

$$H_2C\overset{O}{—}CH_2 + HO^- \longrightarrow HOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$$

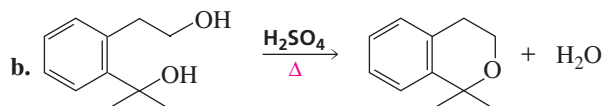
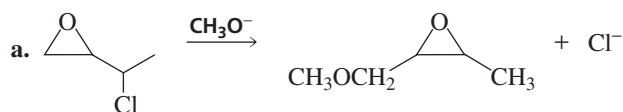
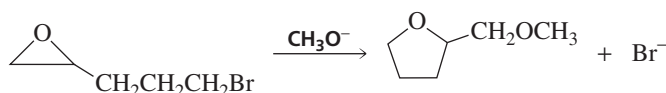
triethylene glycol

44. Explain why more 1-naphthol than 2-naphthol is obtained from the rearrangement of naphthalene oxide.

naphthalene oxide → 1-naphthol 90% + 2-naphthol 10%

45. Propose a mechanism for each of the following reactions:

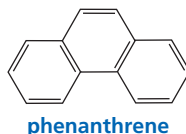
a. Cl (epoxide) $\xrightarrow{CH_3O^-}$ CH_3OCH_2 (epoxide) CH_3 + Cl^-

b. OH, OH $\xrightarrow[\Delta]{H_2SO_4}$ O + H_2O

46. a. Propose a mechanism for the following reaction:

O $CH_2CH_2CH_2Br$ $\xrightarrow{CH_3O^-}$ O CH_2OCH_3 + Br^-

b. A small amount of a product containing a six-membered ring is also formed. Draw the structure of that product.

c. Why is so little six-membered-ring product formed?

47. Three arene oxides can be obtained from phenanthrene.

phenanthrene

a. Draw the structures of the three phenanthrene oxides.

b. What phenols can be obtained from each phenanthrene oxide?

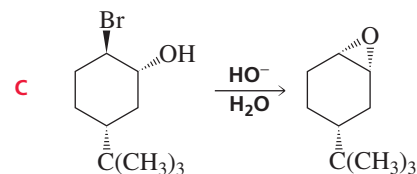
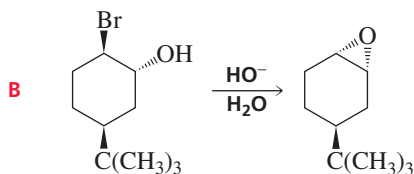
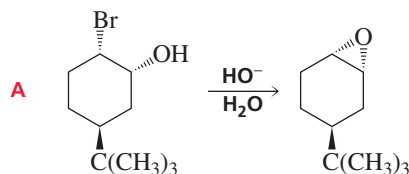
c. If a phenanthrene oxide can lead to the formation of more than one phenol, which phenol is obtained in greater yield?

d. Which of the three phenanthrene oxides is most likely to be carcinogenic?

48. Which of the following reactions occurs most rapidly? Why?

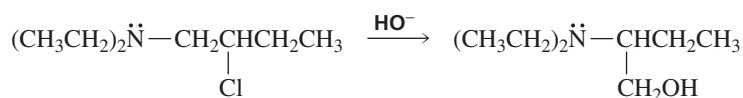
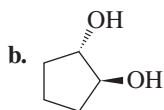
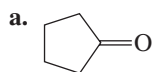
A Br, OH, $C(CH_3)_3$ $\xrightarrow[H_2O]{HO^-}$ O, $C(CH_3)_3$

B Br, OH, $C(CH_3)_3$ $\xrightarrow[H_2O]{HO^-}$ O, $C(CH_3)_3$

C Br, OH, $C(CH_3)_3$ $\xrightarrow[H_2O]{HO^-}$ O, $C(CH_3)_3$

49. The following reaction takes place several times faster than the reaction of 2-chlorobutane with HO^-.

a. Explain the enhanced reaction rate.

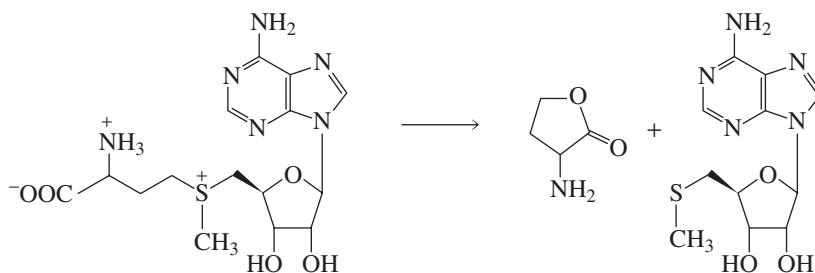
b. Explain why the OH group in the product is not bonded to the carbon that was bonded to the Cl group in the reactant.

$$(CH_3CH_2)_2\ddot{N}-CH_2CH(Cl)CH_2CH_3 \xrightarrow{HO^-} (CH_3CH_2)_2\ddot{N}-CH(CH_2OH)CH_2CH_3$$

50. Show how each of the following compounds could be prepared from chlorocyclopentane.

a. cyclopentanone (=O) **b.** cyclopentane-1,2-diol (OH, OH)

51. Propose a mechanism for the following reaction:

$^-$OOC–CH($\overset{+}{N}H_3$)–CH$_2$CH$_2$–$\overset{+}{S}$(CH$_3$)–(adenosine, HO OH) ⟶ (lactone, NH$_2$, O) + CH$_3$S–(adenosine, HO OH)

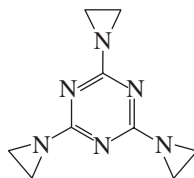
52. Propose a mechanism for the following reaction:

$$\text{cyclopentyl-CH}_2\text{CH}_2\text{OH} \underset{\Delta}{\xrightarrow{H_2SO_4}} \text{alkene} + H_2O$$

53. Explain why the major product obtained from the acid-catalyzed dehydration of 1-butanol is 2-butene.

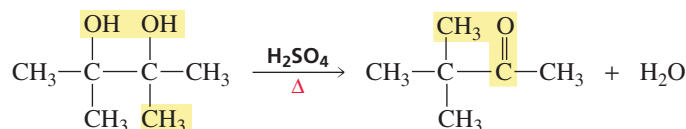
54. What alkenes would you expect to be obtained from the acid-catalyzed dehydration of 1-hexanol?

55. Triethylenemelamine (TEM) is an antitumor agent. Its activity is due to its ability to cross-link DNA.

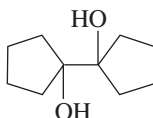
a. Explain why it can be used only under slightly acidic conditions.

b. Explain why it can cross-link DNA.

triethylenemelamine (TEM)

56. When a diol that has OH groups on adjacent carbons undergoes dehydration a rearrangement called a *pinacol rearrangement* occurs. Propose a mechanism for this reaction.

$$CH_3-\underset{CH_3}{\overset{OH}{C}}-\underset{CH_3}{\overset{OH}{C}}-CH_3 \xrightarrow[\Delta]{H_2SO_4} CH_3-\underset{CH_3}{\overset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}-CH_3 + H_2O$$

57. What product is obtained when 2-methyl-1,2-propanediol is heated in an acid solution?

58. What product is obtained when the following diol is heated in an acidic solution?

HO / OH

10 Determining the Structure of Organic Compounds

The red, purple, and blue colors of many flowers, fruits, and vegetables are due to a class of compounds called anthocyanins (see page 391).

Determining the structures of organic compounds is an important part of organic chemistry. Whenever a chemist synthesizes a compound, its structure must be confirmed. For example, you were told that a ketone is formed when an alkyne undergoes the acid-catalyzed addition of water (Section 6.13), but how was it determined that the product of that reaction is actually a ketone? Scientists search the world for new compounds with physiological activity. If a promising compound is found, its structure needs to be determined. Without knowing its structure, chemists cannot design ways to synthesize the compound, nor can they undertake studies to provide insights into its physiological behavior.

Before the structure of a compound can be determined, the compound must be isolated. For example, the product of a reaction carried out in the laboratory must first be isolated from the solvent used to run the reaction, from any unreacted starting materials, and from any side products that might have formed. A compound found in nature must be isolated from the organism that manufactures it.

Isolating products and figuring out their structures used to be daunting tasks. The only tools chemists had for isolating products were distillation (for liquids) and sublimation or fractional recrystallization (for solids). Today, a variety of chromatographic techniques allow compounds to be isolated with relative ease.

There are additional spectroscopy problems in the *Study Guide and Solutions Manual*.

At one time, determining the structure of an organic compound required finding out its molecular formula by elemental analysis, determining the compound's physical properties (its melting point, boiling point, and so on), and conducting simple chemical tests that indicate the presence (or absence) of certain functional groups.

Unfortunately, these simple procedures were inadequate for characterizing molecules with complex structures, and because a relatively large sample of the compound was needed in order to perform all the tests, the tests were impractical for the analysis of compounds that were difficult to obtain in large amounts.

Today, a number of different instrumental techniques are used to identify organic compounds. These techniques can be performed quickly on small amounts of a compound and can provide much more information about the compound's structure than simple chemical tests can give.

- **Mass spectrometry** allows us to determine the *molecular mass* and the *molecular formula* of a compound, as well as some of its *structural features*.
- **Infrared (IR) spectroscopy** tells us the *kinds of functional groups* a compound has.
- **Ultraviolet/Visible (UV/Vis) spectroscopy** provides information about organic compounds with conjugated double bonds.
- **Nuclear magnetic resonance (NMR) spectroscopy** provides information about the carbon–hydrogen framework of an organic compound.

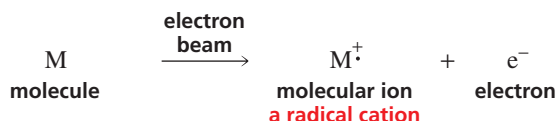
Sometimes more than one technique is required to deduce the structure of a compound. You will find several problems in this chapter that require you to use more than one technique at the same time.

We will be referring to different classes of organic compounds as we discuss various instrumental techniques; they are listed inside the front cover of the book for easy reference.

10.1 MASS SPECTROMETRY

One of the most valuable uses of mass spectrometry is to tell us the molecular weight and molecular formula of a compound. In addition, as we will see, it can tell us some things about the compound's structure.

In mass spectrometry, a small amount of a compound is introduced into an instrument called a mass spectrometer, where it is vaporized and then bombarded by a beam of high-energy electrons. When the electron beam hits a molecule, it knocks out an electron, producing a **molecular ion.** A molecular ion is a **radical cation,** a species with an unpaired electron *and* a positive charge.

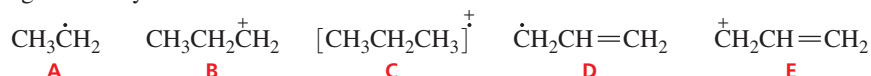
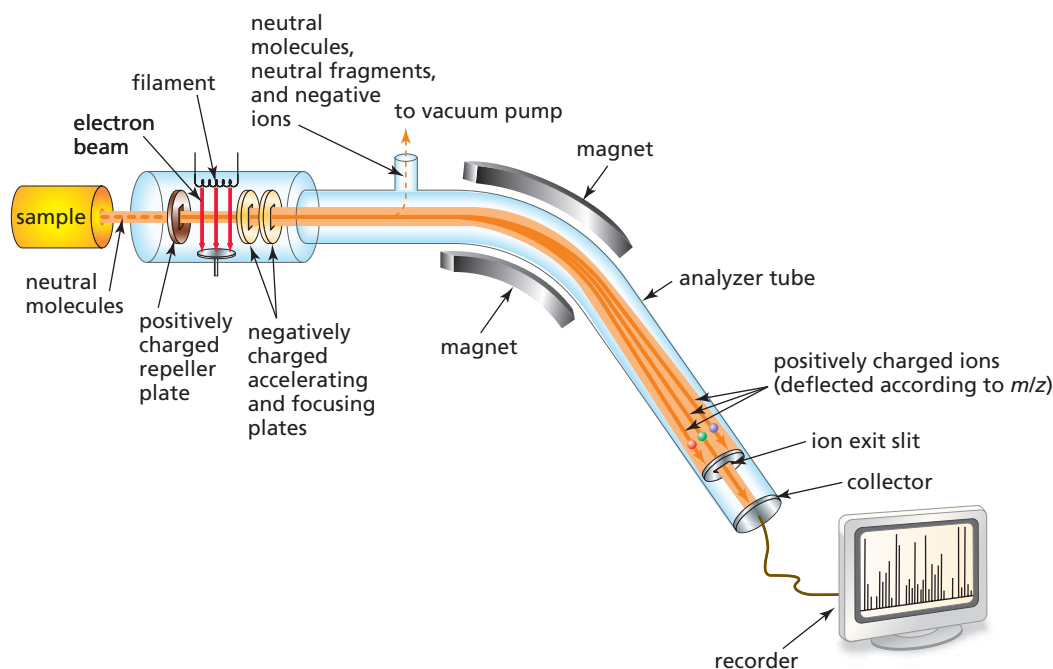
$$\underset{\text{molecule}}{\text{M}} \xrightarrow{\text{electron beam}} \underset{\substack{\text{molecular ion} \\ \text{a radical cation}}}{\text{M}^{\overset{+}{\cdot}}} + \underset{\text{electron}}{e^-}$$

Electron bombardment injects so much kinetic energy into the molecular ions that most of them break apart (fragment) into cations, radicals, neutral molecules, and other radical cations. Not surprisingly, the bonds most likely to break are the weakest ones and those that result in formation of the most stable products.

A mass spectrum records only positively charged fragments.

All the *positively charged fragments* of the molecule are drawn between two negatively charged plates, which accelerate the fragments into an analyzer tube (Figure 10.1). Neutral fragments are not attracted to the negatively charged plates and, therefore, are not accelerated. They are eventually pumped out of the spectrometer.

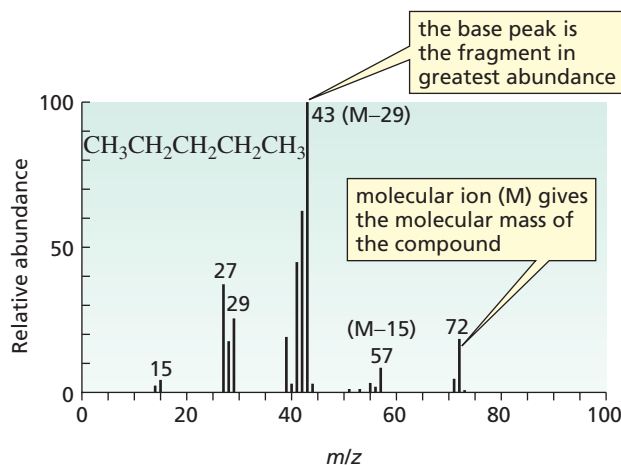
PROBLEM 1♦

Which of the following fragments produced in a mass spectrometer would be accelerated through the analyzer tube?

$CH_3\dot{C}H_2$ (A) $CH_3CH_2\overset{+}{C}H_2$ (B) $[CH_3CH_2CH_3]^{\overset{+}{\cdot}}$ (C) $\dot{C}H_2CH{=}CH_2$ (D) $\overset{+}{C}H_2CH{=}CH_2$ (E)

The mass spectrometer records a **mass spectrum**—a graph of the relative abundance of each fragment plotted against its *m/z* value (Figure 10.2). Because the charge (*z*) on essentially all the fragments that reach the collector plate is +1, *m/z* is the mass (*m*) of the fragment. *Remember that only positively charged species reach the collector.*

▲ **Figure 10.1**
Schematic diagram of a mass spectrometer. A beam of high-energy electrons causes molecules to ionize and fragment. Positively charged fragments pass through the analyzer tube. Changing the magnetic field strength makes it possible to separate fragments of varying mass-to-charge ratios.

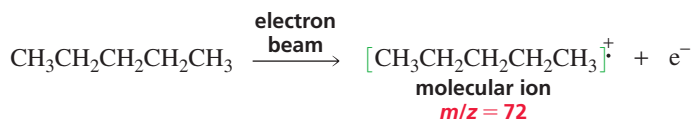
10.2 THE MASS SPECTRUM • FRAGMENTATION

The molecular ion and fragment ions produced in a mass spectrometer and recorded by it are unique for each compound. A mass spectrum, therefore, is like a fingerprint of the compound, so a compound can be identified by comparing its mass spectrum with those of known compounds obtained under the same conditions.

The mass spectrum of pentane is shown in Figure 10.2. Each m/z value in the spectrum is the m/z value of one of the fragments to the nearest whole number. The peak with the highest m/z value in the spectrum—in this case, at $m/z = 72$—is the molecular ion (M), the fragment that results when an electron is knocked out of a molecule. (The extremely tiny peak at $m/z = 73$ will be explained later.) *The m/z value of the molecular ion gives the molecular mass of the compound.*

◀ **Figure 10.2**
The mass spectrum of pentane. The base peak represents the fragment that appears in greatest abundance. The m/z value of the molecular ion (M) gives the molecular mass of the compound.

Because it is not known which bond loses the electron, the molecular ion is written in brackets and the positive charge and unpaired electron are assigned to the entire structure.

The *m/z* value of the molecular ion gives the molecular mass of the compound.

$$CH_3CH_2CH_2CH_2CH_3 \xrightarrow{\text{electron beam}} [CH_3CH_2CH_2CH_2CH_3]^{+\cdot} + e^-$$

molecular ion
$m/z = 72$

Peaks with smaller *m/z* values—called **fragment ion peaks**—represent positively charged fragments of the molecular ion. The **base peak** is the tallest peak, because it has the greatest relative abundance.

The way a molecular ion fragments depends on the strength of its bonds and the stability of the fragments.

A mass spectrum gives us structural information about the compound because the relative abundances of the fragments depend on the strength of the molecular ion's bonds and the stability of the fragments. *Weak bonds break in preference to strong bonds, and bonds that break to form more stable fragments break in preference to those that form less stable fragments.*

Carbocation stability: 3° > 2° > 1° > methyl

Radical stability: 3° > 2° > 1° > methyl

For example, all the C—C bonds in the molecular ion formed from pentane have about the same strength. However, the C-2–C-3 bond is the one most likely to break because it leads to formation of a *primary* carbocation and a *primary* radical, which together are more stable than the *primary* carbocation and *methyl* radical (or *primary* radical and *methyl* cation) obtained from C-1–C-2 fragmentation.

Ions formed by C-2–C-3 fragmentation have *m/z* values of 43 and 29, whereas ions formed by C-1–C-2 fragmentation have *m/z* values of 57 and 15. The base peak of 43 in the mass spectrum of pentane indicates the greater likelihood of C-2–C-3 fragmentation.

See Sections 6.2 and 14.3 to review the relative stabilities of carbocations and radicals, respectively.

C-2–C-3 fragmentation

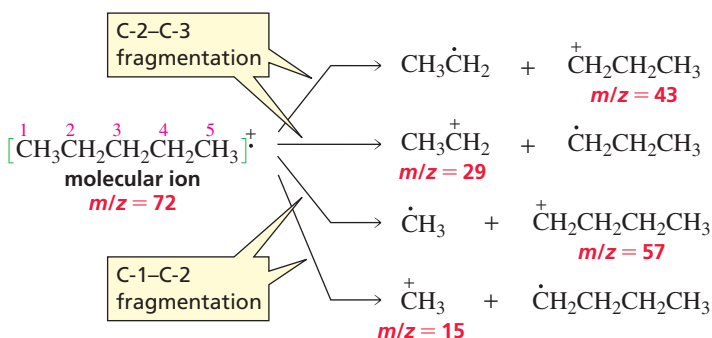
$$[\overset{1}{C}H_3\overset{2}{C}H_2\overset{3}{C}H_2\overset{4}{C}H_2\overset{5}{C}H_3]^{+\cdot}$$
molecular ion
$m/z = 72$

$\rightarrow CH_3\dot{C}H_2 + \overset{+}{C}H_2CH_2CH_3$ ($m/z = 43$)

$\rightarrow CH_3\overset{+}{C}H_2$ ($m/z = 29$) $+ \dot{C}H_2CH_2CH_3$

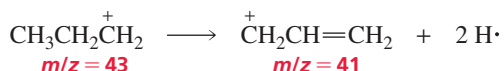
$\rightarrow \dot{C}H_3 + \overset{+}{C}H_2CH_2CH_2CH_3$ ($m/z = 57$)

$\rightarrow \overset{+}{C}H_3$ ($m/z = 15$) $+ \dot{C}H_2CH_2CH_2CH_3$

C-1–C-2 fragmentation

One method for identifying fragment ions makes use of the difference between the *m/z* value of a given fragment ion and that of the molecular ion. For example, the fragment ion with $m/z = 43$ in the mass spectrum of pentane is 29 units smaller than the molecular ion ($72 - 43 = 29$). An ethyl radical (CH_3CH_2) has a mass of 29 (because the mass numbers of C and H are 12 and 1, respectively).

Thus, the peak at 43 can be attributed to loss of an ethyl radical from the molecular ion. Similarly, the fragment ion with $m/z = 57$ can be attributed to loss of a methyl radical from the molecular ion ($72 - 57 = 15$). Peaks at $m/z = 15$ and $m/z = 29$ are readily recognizable as being due to methyl and ethyl cations, respectively.

Peaks are commonly observed at *m/z* values two units below the *m/z* values of the carbocations, because a carbocation can lose two hydrogen atoms.

$$\underset{m/z\,=\,43}{CH_3CH_2\overset{+}{C}H_2} \longrightarrow \underset{m/z\,=\,41}{\overset{+}{C}H_2CH{=}CH_2} + 2\,H\cdot$$

2-Methylbutane has the same molecular formula as pentane. Therefore, it too has a molecular ion with an *m/z* value of 72 (Figure 10.3). Its mass spectrum is similar to that

of pentane, with one notable exception: the peak at $m/z = 57$ indicating loss of a methyl radical is much more intense than the same peak in pentane.

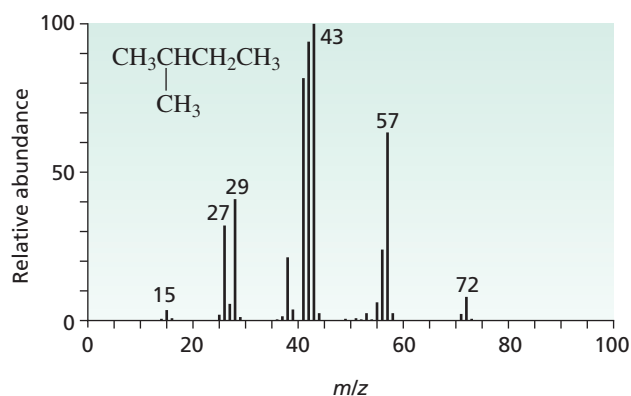
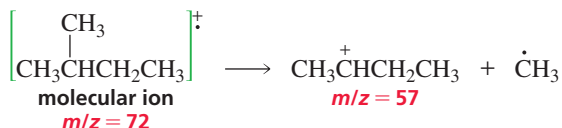



Figure 10.3 The mass spectrum of 2-methylbutane. The peak at $m/z = 57$ corresponds to the loss of a methyl group and the formation of a relatively stable secondary carbocation.

2-Methylbutane is more likely than pentane to lose a methyl radical because, when it does, a *secondary* carbocation is formed. In contrast, when pentane loses a methyl radical, a less stable *primary* carbocation is formed.

$$\left[CH_3\underset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_3\right]^{+\cdot} \longrightarrow CH_3\overset{+}{C}HCH_2CH_3 + \dot{C}H_3$$

molecular ion $m/z = 72$ → $m/z = 57$

PROBLEM 2

What would distinguish the mass spectrum of 2,2-dimethylpropane from the mass spectra of pentane and 2-methylbutane?

PROBLEM 3♦

What is the likeliest *m/z* value for the base peak in the mass spectrum of 3-methylpentane?

10.3 USING THE *m/z* VALUE OF THE MOLECULAR ION TO CALCULATE THE MOLECULAR FORMULA

The **rule of 13** allows possible molecular formulas to be determined from the *m/z* value of the molecular ion. Remember that the *m/z* value of the molecular ion gives the molecular mass of the compound.

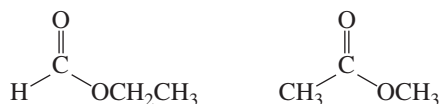
First the **base value** must be determined. To do this, divide the *m/z* value of the molecular ion by 13. The answer gives the number of carbons in the compound. For example, if the *m/z* value is 142, dividing 142 by 13 gives 10 as the number of carbons (with 12 left over). The number of Hs is determined by adding the number left over to the number of carbons ($10 + 12 = 22$). Thus, the base value is $C_{10}H_{22}$.

If the compound has one oxygen, then one O (16 amu) must be added to the base value and one C and four Hs (16 amu) must be subtracted from it. Thus, the molecular formula is $C_9H_{18}O$. If the compound has two oxygens, the process must be repeated, in which case the molecular formula is $C_8H_{14}O_2$. (Notice that in order to maintain the *m/z* value, you need to subtract the same number of atomic mass units that you add.)

PROBLEM 4 Solved

Draw possible structures for an ester that has a molecular ion with an *m/z* value of 74.

Solution Dividing 74 by 13 gives 5 with 9 left over. Thus, the base value is C_5H_{14}. We know that an ester has two oxygens. For each oxygen, add one O and subtract one C and four Hs. This gives a molecular formula of $C_3H_6O_2$. Possible structures are

$$HC(=O)OCH_2CH_3 \qquad CH_3C(=O)OCH_3$$

PROBLEM 5♦

Determine the molecular formula for each of the following:

a. a compound that contains only C and H and has a molecular ion with an *m/z* value of 72
b. a compound that contains C, H, and one O and has a molecular ion with an *m/z* value of 100
c. a compound that contains C, H, and two Os and has a molecular ion with an *m/z* value of 102
d. an amide that has a molecular ion with an *m/z* value of 115

PROBLEM 6♦

Suggest possible molecular formulas for a compound that has a molecular ion with an *m/z* value of 86.

PROBLEM-SOLVING STRATEGY

Using Mass Spectra to Determine Structures

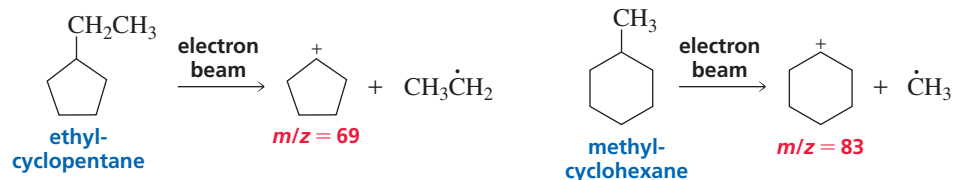
The mass spectra of two very stable cycloalkanes both show a molecular ion peak at $m/z = 98$. One spectrum shows a base peak at $m/z = 69$, whereas the other shows a base peak at $m/z = 83$. Identify the cycloalkanes.

First, let's determine the molecular formula of the compounds from the *m/z* value of their molecular ions. Dividing 98 by 13 results in 7 with 7 left over. Thus, they each have a molecular formula of C_7H_{14}.

Now let's see what fragment is lost to give the base peak. A base peak of 69 means the loss of an ethyl radical $(98 - 69 = 29)$, whereas a base peak of 83 means the loss of a methyl radical $(98 - 83 = 15)$.

Because the two cycloalkanes are known to be very stable, we can assume they do not have three- or four-membered rings. A seven-carbon cycloalkane with a base peak signifying the loss of an ethyl radical must be ethylcyclopentane. A seven-carbon cycloalkane with a base peak signifying the loss of a methyl radical must be methylcyclohexane.

ethylcyclopentane $\xrightarrow{\text{electron beam}}$ cyclopentyl cation ($m/z = 69$) + $CH_3\dot{C}H_2$

methylcyclohexane $\xrightarrow{\text{electron beam}}$ cyclohexyl cation ($m/z = 83$) + $\dot{C}H_3$

Now use the strategy you have just learned to solve Problem 7.

PROBLEM 7♦

Identify the hydrocarbon that has a molecular ion with an *m/z* value of 128, a base peak with an *m/z* value of 43, and significant peaks with *m/z* values of 57, 71, and 85.

10.4 ISOTOPES IN MASS SPECTROMETRY

The molecular ions of pentane and 2-methylbutane both have *m/z* values of 72, but each spectrum shows a very small peak at *m/z* = 73 (Figures 10.2 and 10.3). This peak is called the M+1 peak because the ion responsible for it is one unit heavier than the molecular ion. The M+1 peak owes its presence to the two naturally occurring isotopes of carbon: ^{12}C and ^{13}C (98.89% and 1.11% of naturally occurring carbon, respectively; see Section 1.1). Because mass spectrometry records individual molecules, any molecule containing a ^{13}C will appear at M+1.

The isotopic distributions of several elements commonly found in organic compounds are listed in Table 10.1.

Table 10.1 The Natural Abundance of Isotopes Commonly Found in Organic Compounds

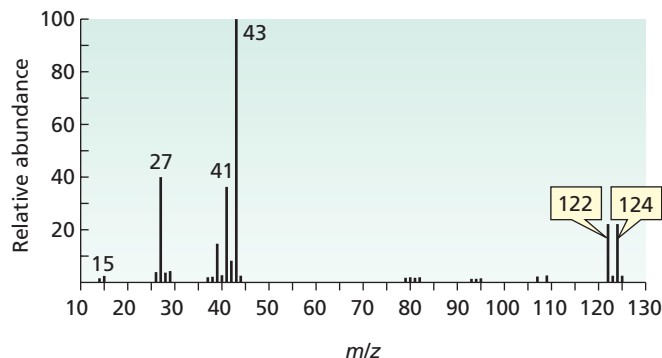
Element	Natural abundance			
Carbon	^{12}C	^{13}C		
	98.89%	1.11%		
Hydrogen	^{1}H	^{2}H		
	99.99%	0.01%		
Nitrogen	^{14}N	^{15}N		
	99.64%	0.36%		
Oxygen	^{16}O	^{17}O	^{18}O	
	99.76%	0.04%	0.20%	
Sulfur	^{32}S	^{33}S	^{34}S	^{36}S
	95.0%	0.76%	4.22%	0.02%
Fluorine	^{19}F			
	100%			
Chlorine	^{35}Cl		^{37}Cl	
	75.77%		24.23%	
Bromine	^{79}Br		^{81}Br	
	50.69%		49.31%	
Iodine	^{127}I			
	100%			

Mass spectra can also show M+2 peaks due to ^{18}O or from having two heavy isotopes in the same molecule (such as ^{13}C and ^{2}H, or two ^{13}Cs). These situations are unusual, though, so the M+2 peaks tend to be very small. The presence of a large M+2 peak is evidence of a compound containing either chlorine or bromine, because each of these elements has a high percentage of a naturally occurring isotope that is two units heavier than the most abundant isotope.

From the natural abundance of the isotopes of chlorine and bromine in Table 10.1, we can conclude that if the M+2 peak is one-third the height of the molecular ion peak, then the compound contains a chlorine atom because the natural abundance of ^{37}Cl is one-third that of ^{35}Cl. If the M and M+2 peaks are about the same height, then the compound contains a bromine atom because the natural abundances of ^{79}Br and ^{81}Br are about the same.

In calculating the *m/z* values of molecular ions and fragments, the *atomic mass* of a single isotope of the atom must be used (for example, Cl = 35 or 37) because mass spectrometry records the *m/z* value of an *individual* fragment. The *atomic weights* in the periodic table (Cl = 35.453) cannot be used, because they are the *weighted averages* of all the naturally occurring isotopes for that element.

PROBLEM 8♦

Identify the primary alkyl halide responsible for the mass spectrum shown here.

PROBLEM 9

Sketch the mass spectrum of 1-chloropropane.

10.5 HIGH-RESOLUTION MASS SPECTROMETRY CAN REVEAL MOLECULAR FORMULAS

All the mass spectra shown in this book were produced with a low-resolution mass spectrometer. Such spectrometers give the *m/z* value of a fragment to the nearest whole number. High-resolution mass spectrometers can determine the *exact molecular mass* of a fragment to a precision of 0.0001 amu, making it possible to distinguish between compounds that have the same molecular mass to the nearest whole number. For example, the following listing shows six compounds that have a molecular mass of 122 amu, but each of them has a different exact molecular mass.

Some Compounds with a Molecular Mass of 122 amu and Their Exact Molecular Masses and Molecular Formulas

Exact molecular mass (amu)	122.1096	122.0845	122.0732	122.0368	122.0579	122.0225
Molecular formula	C_9H_{14}	$C_7H_{10}N_2$	$C_8H_{10}O$	$C_7H_6O_2$	$C_4H_{10}O_4$	$C_4H_{10}S_2$

The exact masses of some common isotopes are listed in Table 10.2. There are computer programs that can determine the molecular formula of a compound from the compound's exact molecular mass.

Table 10.2 The Exact Masses of Some Common Isotopes

Isotope	Mass
^{1}H	1.007825 amu
^{12}C	12.00000 amu
^{14}N	14.0031 amu
^{16}O	15.9949 amu
^{32}S	31.9721 amu
^{35}Cl	34.9689 amu
^{79}Br	78.9183 amu

PROBLEM 10♦

Which molecular formula has an exact molecular mass of 86.1096 amu: C_6H_{14}, $C_4H_{10}N_2$, or $C_4H_6O_2$?

PROBLEM 11♦

a. Can a low-resolution mass spectrometer distinguish between $C_2H_5^+$ and CHO^+?
b. Can a high-resolution mass spectrometer distinguish between them?

10.6 FRAGMENTATION PATTERNS

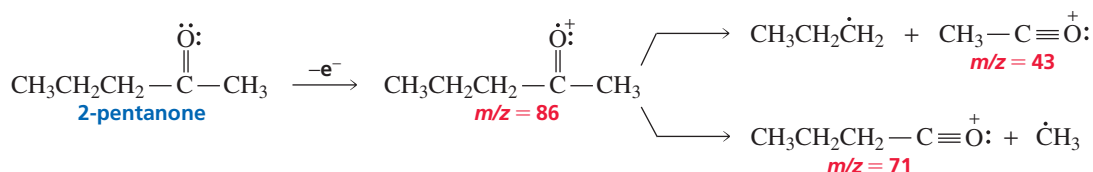
Each functional group has characteristic fragmentation patterns that can help identify a compound. The patterns began to be recognized after the mass spectra of many compounds containing a particular functional group had been studied. We will look at the fragmentation patterns of ketones as an example.

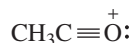
Electron bombardment is most likely to dislodge a lone-pair electron, if a molecule has any, because a molecule does not hold onto its lone-pair electrons as tightly as it holds onto its bonding electrons. Therefore, when a ketone is bombarded by electrons, the molecular ion is formed when one of oxygen's lone-pair electrons is knocked out of the molecule.

$$CH_3CH_2CH_2-\overset{\overset{\displaystyle :\ddot{O}:}{\|}}{C}-CH_3 \xrightarrow{-e^-} CH_3CH_2CH_2-\overset{\overset{\displaystyle \dot{O}:^+}{\|}}{C}-CH_3$$

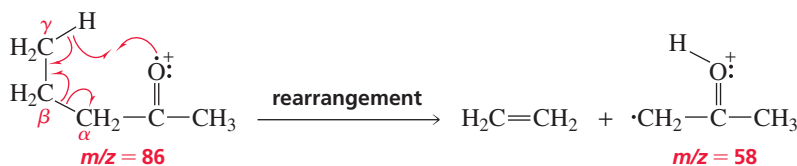
2-pentanone; *m/z* = 86

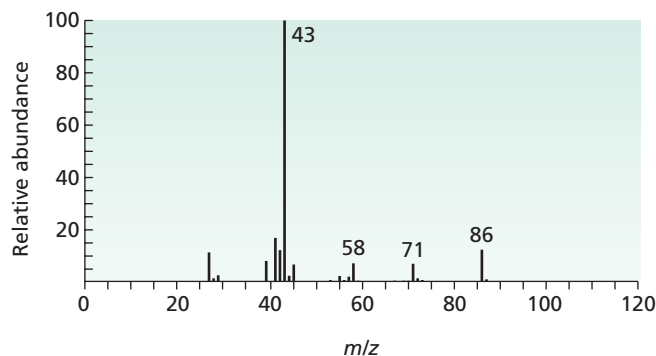
$$\longrightarrow CH_3CH_2\dot{C}H_2 + CH_3-C\equiv\overset{+}{O}: \quad m/z = 43$$

$$\longrightarrow CH_3CH_2CH_2-C\equiv\overset{+}{O}: + \dot{C}H_3 \quad m/z = 71$$

The molecular ion fragments at the C—C bond adjacent to the C=O bond, with each of the carbons retaining one of the electrons. The C—C bond is the bond most easily broken because the species that is formed is a relatively stable cation, since all its atoms have complete octets.

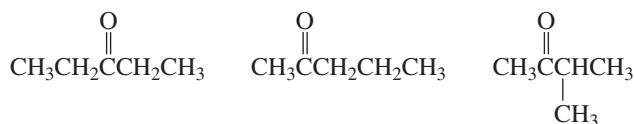
$$CH_3C\equiv\overset{+}{O}:$$

If one of the alkyl groups attached to a carbonyl carbon has a γ-hydrogen, a fragmentation, which goes through a favorable six-membered-ring transition state, may occur. In this rearrangement, the bond between the α-carbon and the β-carbon breaks, with each of the carbons retaining one of the electrons, and a hydrogen atom from the γ-carbon migrates to the oxygen atom. This fragmentation occurs because it forms ethene—a stable molecule.

An arrowhead with one barb represents the movement of one electron.

$$\underset{m/z\,=\,86}{H_2C^{\gamma}(H)-H_2C^{\beta}-CH_2^{\alpha}-\overset{\overset{\displaystyle \dot{O}:^+}{\|}}{C}-CH_3} \xrightarrow{\text{rearrangement}} H_2C=CH_2 + \underset{m/z\,=\,58}{\cdot CH_2-\overset{\overset{\displaystyle H-\overset{+}{O}:}{\|}}{C}-CH_3}$$

PROBLEM 12

Identify the ketone responsible for the mass spectrum shown here.

PROBLEM 13

How could their mass spectra distinguish the following compounds?

$$CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_3 \qquad CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_3 \qquad CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{CH_3}{|}}{C}HCH_3$$

10.7 GAS CHROMATOGRAPHY–MASS SPECTROMETRY

Mixtures of compounds are often analyzed using gas chromatography and mass spectrometry (GC–MS) at the same time. The sample is injected into a gas chromatograph and the various components of the mixture travel through the column at different rates, based on their boiling points. The lowest boiling component of the mixture exits first. As each compound exits, it enters the mass spectrometer, where it is ionized, forming a molecular ion and fragments of the molecular ion. The mass spectrometer records a mass spectrum for each of the components of the mixture. GC–MS is widely used to analyze forensic samples.

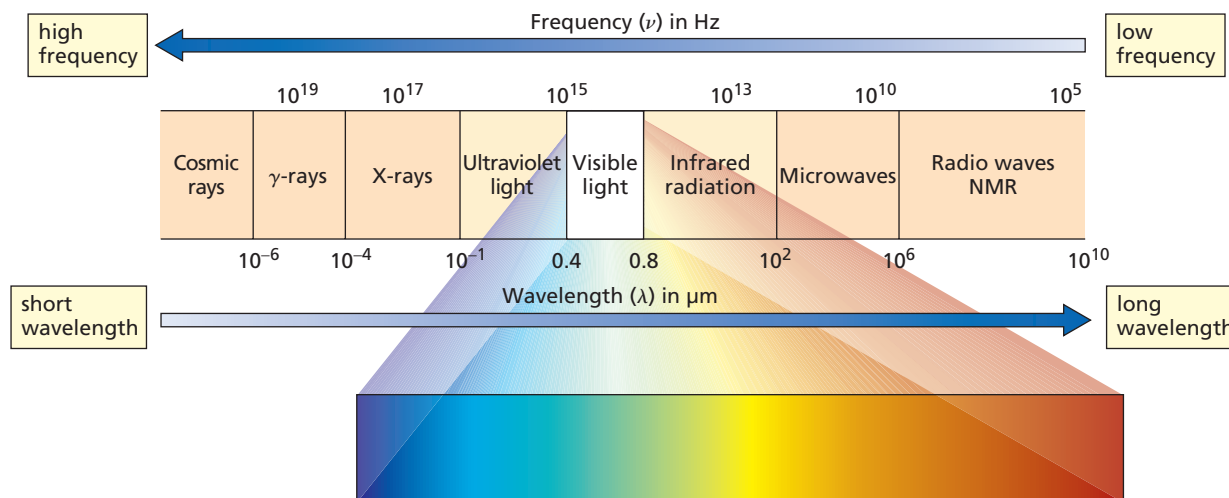
Mass Spectrometry in Forensics

Forensic science is the application of science for the purpose of answering questions related to a civil or criminal case. Mass spectrometry is an important tool of the forensic scientist. It is used to analyze body fluids for the presence and levels of drugs and other toxic substances. It can also identify the presence of drugs in hair, which increases the window of detection from hours and days (after which body fluids are no longer useful) to months and even years. It was employed for the first time at an athletic event in 1955 to detect drugs in athletes at a cycling competition in France. (Twenty percent of those tests were positive.) Mass spectrometry is also used to identify residues of arson fires and explosives from post-explosion residues, as well as to analyze such things as paints, adhesives, and fibers.

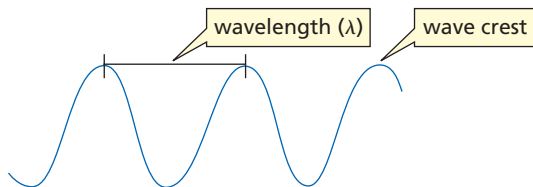
10.8 SPECTROSCOPY AND THE ELECTROMAGNETIC SPECTRUM

Spectroscopy is the study of the interaction of matter and electromagnetic radiation. A continuum of different types of **electromagnetic radiation**—each associated with a particular energy range—makes up the electromagnetic spectrum (Figure 10.4). Visible light is the electromagnetic radiation we are most familiar with, but it represents only a fraction of the full electromagnetic spectrum. X-rays, microwaves, and radio waves are other familiar types of electromagnetic radiation.

The various kinds of electromagnetic radiation can be characterized briefly as follows:

- *Cosmic rays* are discharged by the sun; they have the highest energy of the various kinds of electromagnetic radiation.
- *γ-Rays* (gamma rays) are emitted by the nuclei of certain radioactive elements. Because of their high energy, they can severely damage biological organisms.
- *X-Rays*, somewhat lower in energy than γ-rays, are less harmful, except in high doses. Low-dose X-rays are used to examine the internal structure of organisms. The denser the tissue, the more it blocks X-rays.

▲ **Figure 10.4**
The electromagnetic spectrum. Electromagnetic radiation with the highest energy (the highest frequency and the shortest wavelength) is located on the left, whereas electromagnetic radiation with the lowest energy (the lowest frequency and the longest wavelength) is located on the right.

- *Ultraviolet (UV) light*, a component of sunlight, causes sunburns, and repeated exposure to it can cause skin cancer by damaging DNA molecules in skin cells.
- *Visible light* is the electromagnetic radiation we see.
- We feel *infrared radiation* as heat.
- We cook with *microwaves* and use them in radar.
- *Radio waves* have the lowest energy of the various kinds of electromagnetic radiation. We use them for radio and television communication, digital imaging, garage door openers, and wireless linkages for computers. Radio waves are also used in NMR spectroscopy and in magnetic resonance imaging (MRI).

Because electromagnetic radiation has wave-like properties, it can be characterized, as a wave can, by either its frequency (ν) or its wavelength (λ). **Frequency** is defined as the number of wave crests that pass by a given point in one second. **Wavelength** is the distance from any point on one wave to the corresponding point on the next wave.

The relationship between the energy (E) and the frequency (ν) or wavelength (λ) of the electromagnetic radiation is described by the equation

$$E = h\nu = \frac{hc}{\lambda}$$

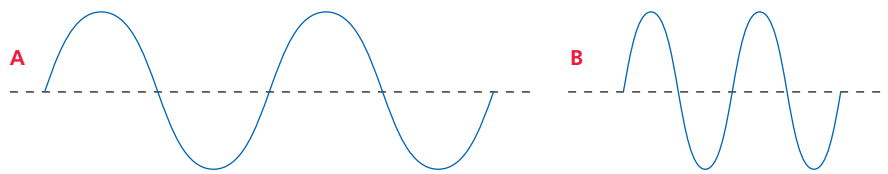
where h is *Planck's constant*, a proportionality constant named after the German physicist who discovered the relationship, and c is the speed of light ($c = 3.0 \times 10^{10}$ cm/s). The equation shows that short wavelengths have high energies and high frequencies, and long wavelengths have low energies and low frequencies.

Another way to describe the *frequency* of the electromagnetic radiation—and the one most often used in infrared spectroscopy—is **wavenumber** ($\tilde{\nu}$), which is the number of waves in 1 cm. Wavenumbers, therefore, have units of reciprocal centimeters (cm^{-1}).

High frequencies, large wavenumbers, and *short wavelengths* are associated with *high energies.*

PROBLEM 14♦

One of the following depicts the waves associated with infrared radiation, and one depicts the waves associated with visible light. Which is which?

High frequencies, large wavenumbers, and short wavelengths are associated with high energies.

PROBLEM 15♦

a. Which is higher in energy: electromagnetic radiation with wavenumber 100 cm^{-1} or with wavenumber 2000 cm^{-1}?

b. Which is higher in energy: electromagnetic radiation with wavelength 9 μm or with wavelength 8 μm?

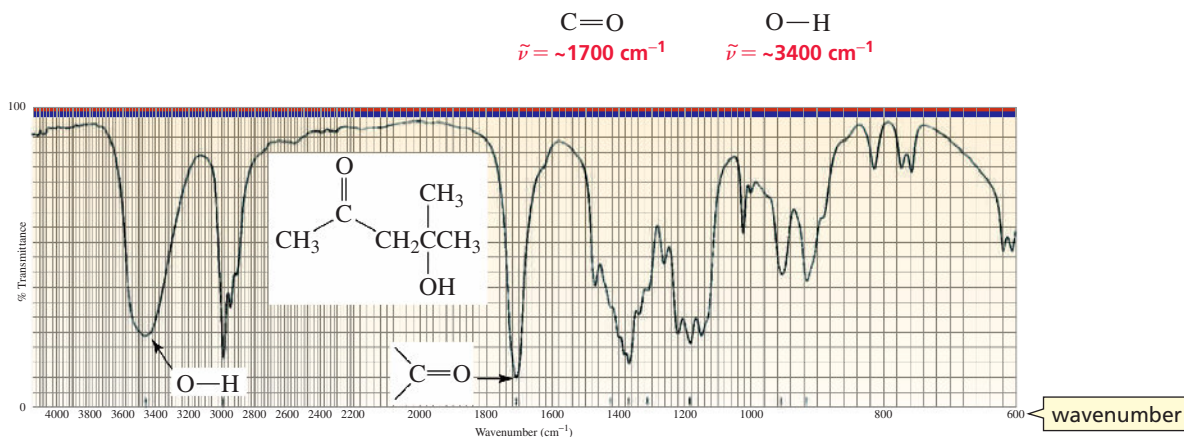
10.9 INFRARED SPECTROSCOPY

The length reported for a bond between two atoms is an average length, because in reality a bond behaves as if it were a vibrating spring. A bond vibrates with both stretching and bending motions.

A *stretch* is a vibration occurring along the line of the bond; a stretching vibration changes the bond length.

A *bend* is a vibration that does *not* occur along the line of the bond; a bending vibration changes the bond angle.

Each stretching and bending vibration of a given bond occurs with a characteristic frequency. When a molecule is bombarded with radiation of a frequency that exactly matches the frequency of the vibration of one of its bonds, the molecule absorbs energy. This allows the bond to stretch and bend a bit more. By experimentally determining the wavenumbers of the energy absorbed by a particular compound, we can ascertain what kinds of bonds it has. For example, the stretching vibration of a C=O bond absorbs energy with wavenumber ~1700 cm^{-1}, whereas the stretching vibration of an O—H bond absorbs energy with wavenumber ~3400 cm^{-1} (Figure 10.5).

C=O $\tilde{\nu}$ = ~1700 cm^{-1} O—H $\tilde{\nu}$ = ~3400 cm^{-1}

▲ **Figure 10.5**
An infrared spectrum shows the percent transmission of radiation versus the wavenumber of the radiation. The (C=O) stretch absorbs at 1705 cm^{-1} and the (O—H) stretch absorbs at 3450 cm^{-1}.

10.10 CHARACTERISTIC INFRARED ABSORPTION BANDS

IR spectra can be quite complex because the stretching and bending vibrations of each bond in a molecule can produce an absorption band. Organic chemists, however, do not try to identify all the absorption bands in an IR spectrum. They tend to focus on the functional groups. In this chapter, we will look at several characteristic absorption bands so you will be able to tell something about the structure of a compound that gives a particular IR spectrum.

More energy is required to stretch a bond than to bend it, so absorption bands for stretching vibrations are found in the higher-energy region (4000−1400 cm^{-1}), whereas those for bending vibrations are typically found in the lower-energy region (1400−600 cm^{-1}). Stretching vibrations are the ones most often used to determine what kinds of bonds a molecule has. The *frequencies of the stretching vibrations* associated with different types of bonds (and their intensities) are listed in Table 10.3.

It takes more energy to stretch a bond than to bend it, so stretching vibrations are found at higher wavenumbers than bending vibrations.

Table 10.3 Frequencies of Important IR Stretching Vibrations

Type of bond	Wavenumber (cm^{-1})	Intensity
C≡N	2260–2220	medium
C≡C	2260–2100	medium to weak
C═C	1680–1600	medium
C═N	1650–1550	medium
(benzene ring)	~1600 and ~1500–1430	strong to weak
C═O	1780–1650	strong
C—O	1250–1050	strong
C—N	1230–1020	medium
O—H (alcohol)	3650–3200	strong, broad
O—H (carboxylic acid)	3300–2500	strong, very broad
N—H	3500–3300	medium, broad
C—H	3300–2700	medium

10.11 THE INTENSITY OF ABSORPTION BANDS

When a bond stretches, the increasing distance between the atoms increases its dipole moment. The intensity of the absorption band depends on the size of this change in dipole moment: *the greater the change in dipole moment, the more intense the absorption*.

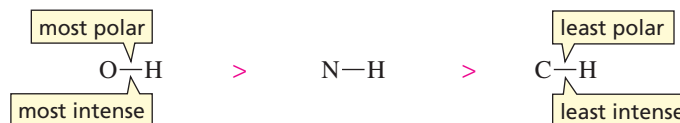
For example, absorption bands for the stretching vibrations of C═O and C═C bonds appear at similar frequencies, but they are easily distinguished: the one for C═O is much more intense because it is associated with a much greater change in dipole moment since the bond is more polar. (Compare the C═O absorption bands in Figures 10.6–10.9 with the C═C absorption band in Figure 10.14.)

The stretching vibration of an O—H bond is associated with a greater change in dipole moment than that of an N—H bond, because the O—H bond is more polar. Consequently, an O—H bond shows more intense absorption than an N—H bond. Similarly, an N—H bond shows more intense absorption than a C—H bond, because the N—H bond is more polar.

Recall that the dipole moment of a bond is equal to the *magnitude of the charge* on one of the bonded atoms multiplied by the *distance* between the two bonded atoms (Section 1.3).

The greater the change in the dipole moment, the more intense the absorption.

The more polar the bond, the more intense the absorption.

relative bond polarities
relative intensities of IR absorption

The intensity of an absorption band also depends on the number of bonds responsible for the absorption. For example, the absorption band for a C—H stretch will be more intense for a compound such as octyl iodide, which has 17 C—H bonds, than for methyl iodide, which has only 3 C—H bonds.

10.12 THE POSITION OF ABSORPTION BANDS

The frequency of a stretching vibration—the amount of energy required to stretch a bond—depends on the *strength* of the bond. The stronger the bond, the greater the energy required to stretch it.

Bond order—whether a bond is a single bond, a double bond, or a triple bond—affects bond strength. Therefore, bond order affects the position of absorption bands.

Stronger bonds show absorption bands at larger wavenumbers.

C≡N
~2200 cm^{-1}
C═N
~1600 cm^{-1}
C—N
~1100 cm^{-1}

A C≡C bond is stronger than a C═C bond, so a C≡C bond stretches at a higher frequency (~2100 cm^{-1}) than does a C═C bond (~1650 cm^{-1}); C—C bonds show stretching vibrations in the region from 1300 to 800 cm^{-1}, but since they are weak and very common, these vibrations are of little value in identifying organic compounds.

Similarly, a C═O bond stretches at a higher frequency (~1700 cm^{-1}) than does a C—O bond (~1100 cm^{-1}), and a C≡N bond stretches at a higher frequency (~2200 cm^{-1}) than does a C═N bond (~1600 cm^{-1}), which in turn stretches at a higher frequency than does a C—N bond (~1100 cm^{-1}) (Table 10.3).

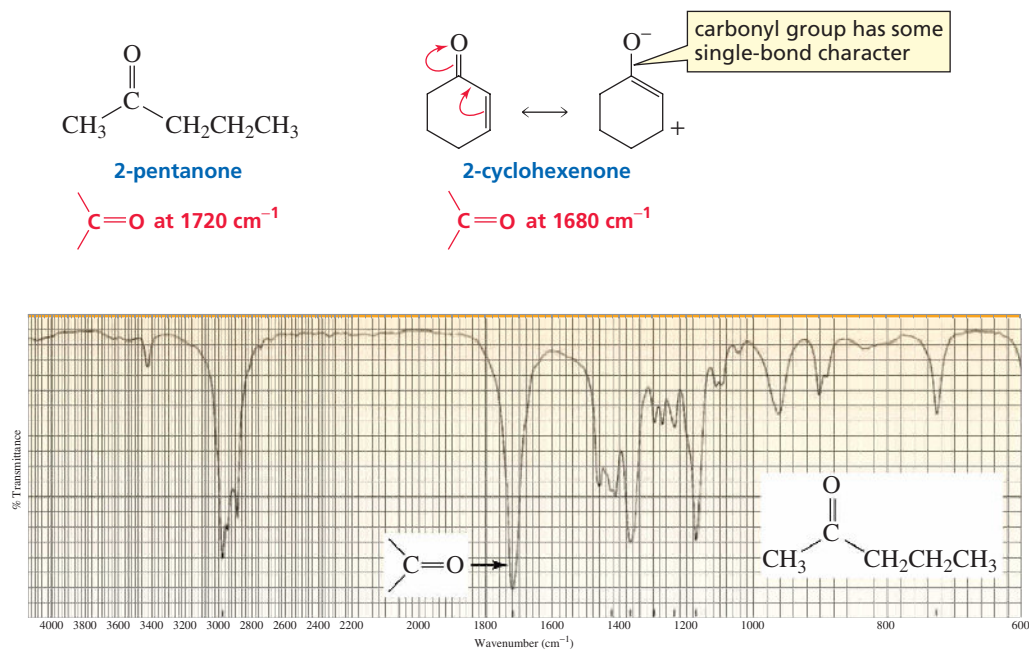
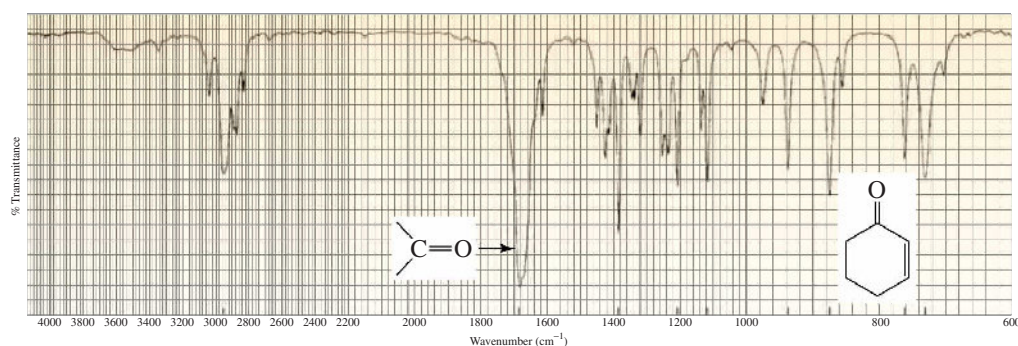
PROBLEM 16♦

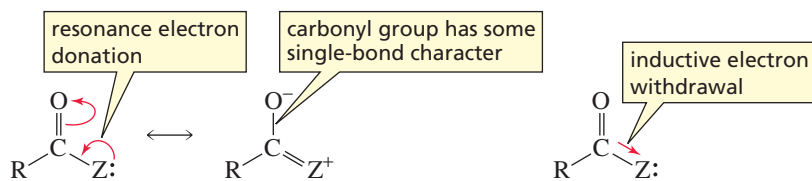
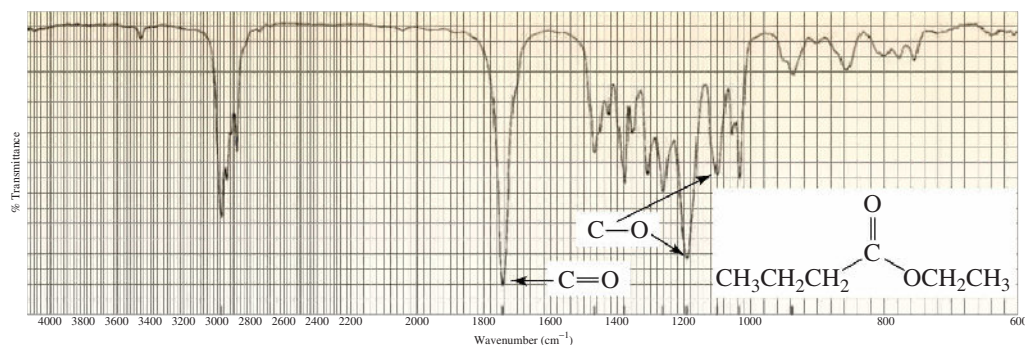
Which will occur at a larger wavenumber:

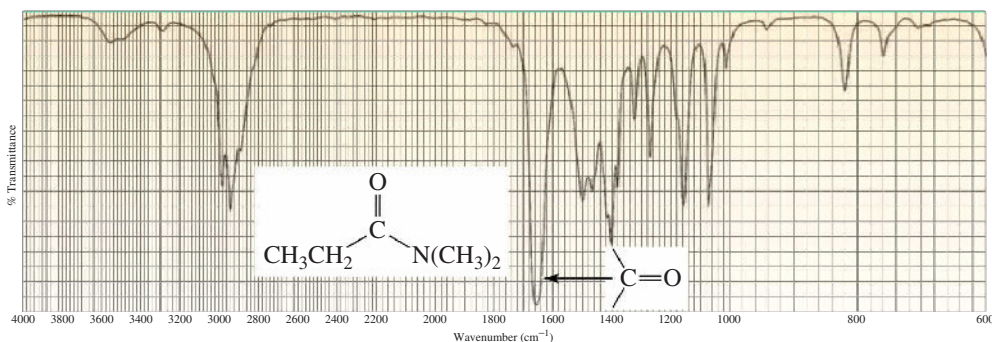
a. a C≡C stretch or a C═C stretch?
b. a C—H stretch or a C—H bend?
c. a C—N stretch or a C═N stretch?
d. a C═O stretch or a C—O stretch?

10.13 THE POSITION AND SHAPE OF AN ABSORPTION BAND IS AFFECTED BY ELECTRON DELOCALIZATION, ELECTRON DONATION AND WITHDRAWAL, AND HYDROGEN BONDING

Table 10.3 shows a range of wavenumbers for the frequency of the stretching vibration for each functional group because the exact position and shape of a group's absorption band depends on other structural features of the molecule, such as electron delocalization, the electronic effect of neighboring substituents, and hydrogen bonding. In fact, important details about the structure of a compound can be revealed by the exact positions and shape of its absorption bands.

For example, the IR spectrum in Figure 10.6 shows that the carbonyl group (C═O) of 2-pentanone absorbs at 1720 cm^{-1}, whereas the IR spectrum in Figure 10.7 shows that the carbonyl group of 2-cyclohexenone absorbs at a lower frequency (1680 cm^{-1}). 2-Cyclohexenone's carbonyl group absorbs at a lower frequency because it has more single-bond character due to electron delocalization. A single bond is weaker than a double bond, so a carbonyl group with significant single-bond character will stretch at a lower frequency than will one with little or no single-bond character.

▲ Figure 10.6
The intense absorption band at ~1720 cm^{-1} indicates a C=O bond.

▲ Figure 10.7
Electron delocalization gives the carbonyl group less double-bond character, so it absorbs at a lower frequency (~1680^{-1}) than does a carbonyl group with localized electrons (~1720 cm^{-1}).

Putting an atom other than carbon next to the carbonyl group also causes the position of the carbonyl absorption band to shift. Whether it shifts to a lower or to a higher frequency depends on whether the predominant effect of the atom is to donate electrons by resonance or to withdraw electrons inductively.

The predominant effect of the nitrogen of an amide is electron donation by resonance. In contrast, oxygen is less able than nitrogen to accommodate a positive charge because of oxygen's greater electronegativity, so the predominant effect of the oxygen of an ester is inductive electron withdrawal (Sections 2.7 and 7.9). As a result, the carbonyl group of an ester has less single-bond character, so it requires more energy to stretch (1740 cm^{-1} in Figure 10.8) than the carbonyl group of an amide (1660 cm^{-1} in Figure 10.9).

▲ **Figure 10.8**
The electron-withdrawing oxygen atom makes the carbonyl group of an ester harder to stretch (~1740 cm^{-1}) than the carbonyl group of a ketone (~1720 cm^{-1}).

▶ **Figure 10.9**
The carbonyl group of an amide has less double-bond character than the carbonyl group of a ketone, so the carbonyl group of an amide stretches more easily (~1660 cm^{-1}) than the carbonyl group of a ketone (~1720 cm^{-1}).

PROBLEM-SOLVING STRATEGY

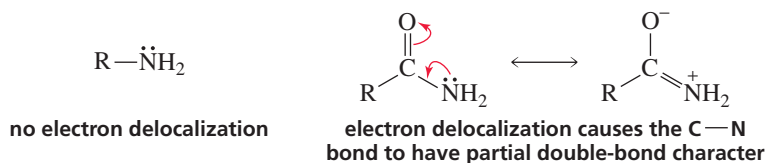
Differences in IR Spectra

Which will occur at a larger wavenumber: the C—N stretch of an amine or the C—N stretch of an amide?

To answer this question, we need to determine what effect electron delocalization has on the C—N bond in amines and amides. When we do that we see that the C—N bond of the amine is a pure single bond, whereas electron delocalization causes the C—N bond of the amide to have partial double-bond character. The C—N stretch of an amide, therefore, will occur at a larger wavenumber.

$R-\ddot{N}H_2$ **no electron delocalization**

$R-C(=O)-\ddot{N}H_2 \longleftrightarrow R-C(-O^-)=\overset{+}{N}H_2$

electron delocalization causes the C—N bond to have partial double-bond character

Now use the strategy you have just learned to solve Problem 17.

PROBLEM 17♦

Which will occur at a larger wavenumber:

a. the C—O stretch of phenol or the C—O stretch of cyclohexanol?
b. the C=O stretch of a ketone or the C=O stretch of an amide?
c. the C—N stretch of cyclohexylamine or the C—N stretch of aniline?

PROBLEM 18♦

Which would show an absorption band at a larger wavenumber: a carbonyl group bonded to an sp^3 carbon or a carbonyl group bonded to an sp^2 carbon of an alkene?

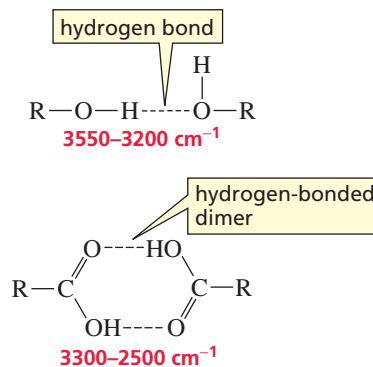
PROBLEM 19♦

Why is the C—O absorption band of 1-hexanol at a smaller wavenumber (1060 cm^{-1}) than the C—O absorption band of pentanoic acid (1220 cm^{-1})?

O—H and N—H Absorption Bands

Because O—H bonds are polar, they show intense absorption bands that can be quite broad (Figures 10.10 and 10.11). Both the position and the shape of an O—H absorption band depend on hydrogen bonding. It is easier for an O—H bond to stretch if it is hydrogen bonded, because the hydrogen is attracted to the oxygen of a neighboring molecule. Hydrogen-bonded OH groups have broader absorption bands because hydrogen bonds vary in strength, and bonds with different strengths absorb at different frequencies.

Carboxylic acids can exist as hydrogen-bonded dimers. The additional hydrogen bonding of carboxylic acids (Figure 10.10) compared with the hydrogen bonding of alcohols (Figure 10.11) causes the O—H stretch of a carboxylic acid to occur at a lower frequency and to be broader (3300–2500 cm^{-1}) than the O—H stretch of an alcohol (3550–3200 cm^{-1}).

N—H bonds are less polar and form weaker hydrogen bonds than do O—H bonds, so the absorption band for an N—H stretch is less intense and narrower than that for an O—H stretch (Figure 10.12),

The position, intensity, and shape of an absorption band are helpful in identifying functional groups.

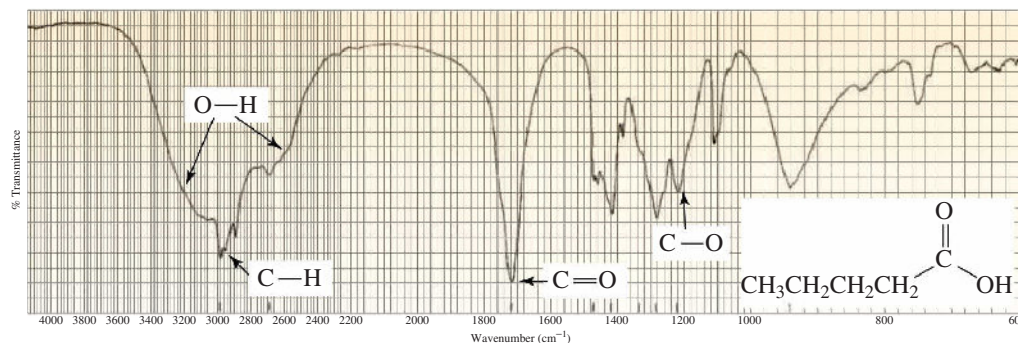



Figure 10.10
The IR spectrum of pentanoic acid.

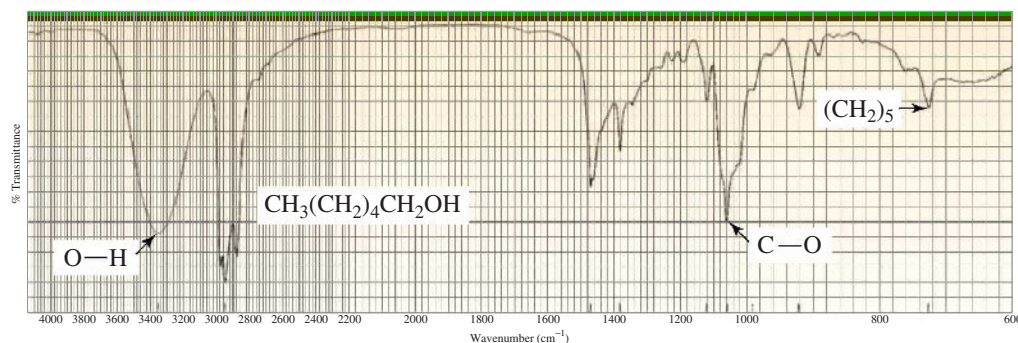



Figure 10.11
The IR spectrum of 1-hexanol.

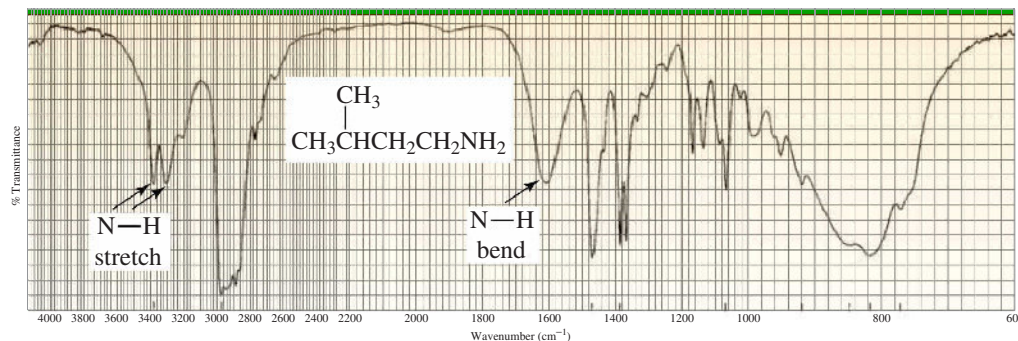



Figure 10.12
The IR spectrum of isopentylamine. The N—H bend around 1600 cm^{-1} is broad due to intermolecular hydrogen bonding.

PROBLEM 20♦

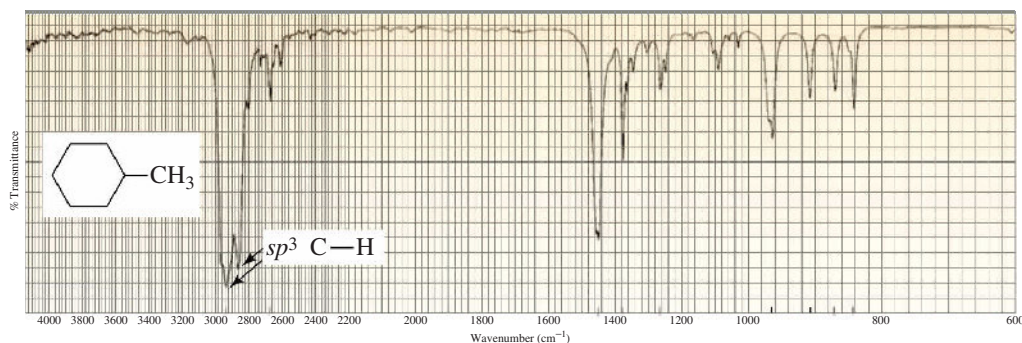
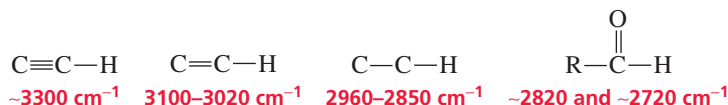
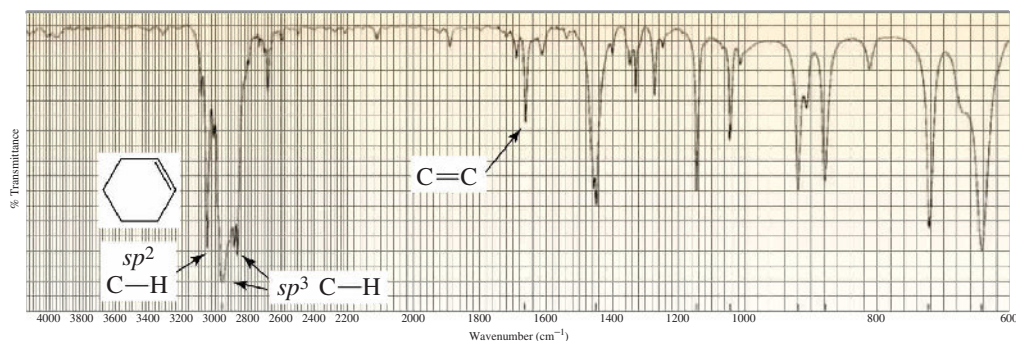
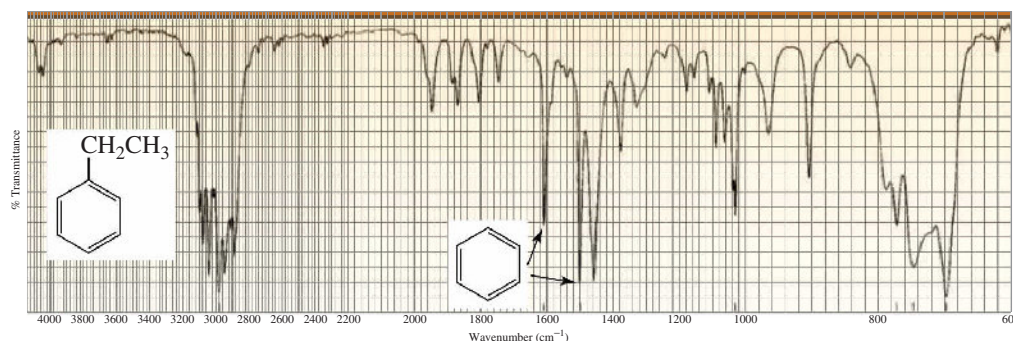
Which will show an O—H stretch at a larger wavenumber: ethanol dissolved in carbon disulfide or an undiluted sample of ethanol?

C—H Absorption Bands

Important information about the identity of a compound is provided by the stretching vibrations of its C—H bonds.

The strength of a C—H bond depends on the hybridization of the carbon. A C—H bond is stronger when the carbon is *sp* hybridized than when it is sp^2 hybridized, which in turn is stronger than when the carbon is sp^3 hybridized (see Table 1.7 on page 61). Because more energy is needed to stretch a stronger bond, the absorption band for a C—H stretch is at ~3300 cm^{-1} for an *sp* carbon, at ~3100 cm^{-1} for an sp^2 carbon, and at ~2900 cm^{-1} for an sp^3 carbon.

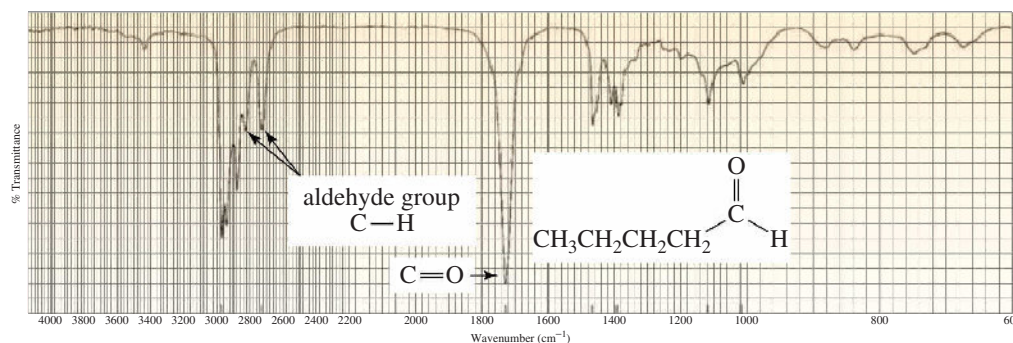
A useful step in the analysis of an IR spectrum is to look at the absorption bands in the vicinity of 3000 cm^{-1}. The only absorption band in the vicinity of 3000 cm^{-1} in Figure 10.13 is slightly to the right of that value. This tells us that the compound has hydrogens bonded to sp^3 carbons, but none bonded to sp^2 or to *sp* carbons. Both Figures 10.14 and 10.15 show absorption bands slightly to the left and slightly to the right of 3000 cm^{-1}, indicating that the compounds that produced those spectra contain hydrogens bonded to both sp^2 and sp^3 carbons.

C≡C—H	C=C—H	C—C—H	R—C(=O)—H
~3300 cm^{-1}	3100–3020 cm^{-1}	2960–2850 cm^{-1}	~2820 and ~2720 cm^{-1}

▲ Figure 10.13
The IR spectrum of methylcyclohexane. The absorptions at 2940 and 2860 cm^{-1} indicate that methylcyclohexane has hydrogens bonded to sp^3 carbons.

▲ Figure 10.14
The IR spectrum of cyclohexene. The absorptions at 3040, 2950, and 2860 cm^{-1} indicate that cyclohexene has hydrogens bonded to both sp^2 and sp^3 carbons.

▲ Figure 10.15

The IR spectrum of ethylbenzene. The absorptions in the 3100–2880 cm^{-1} region indicate that ethylbenzene has hydrogens bonded to both sp^2 and sp^3 carbons. The two sharp absorptions at 1610 and 1500 cm^{-1} indicate that the sp^2 carbons are those of a benzene ring.

Once we know that a compound has hydrogens bonded to sp^2 carbons, we need to determine whether those carbons are the sp^2 carbons of an alkene or of a benzene ring. A benzene ring is indicated by two sharp absorption bands, one at ~1600 cm^{-1} and one at 1500−1430 cm^{-1}, whereas an alkene is indicated by a band only at ~1600 cm^{-1} (Table 10.3). The compound whose spectrum is shown in Figure 10.14 is, therefore, an alkene, whereas the one whose spectrum is shown in Figure 10.15 has a benzene ring. (If you have an NMR spectrum of the compound, the presence of a benzene ring is very easy to detect; see Section 10.28).

Be aware that N—H bending vibrations also occur at 1600 cm^{-1}, so absorption at that wavelength does not always indicate a C═C bond. However, absorption bands resulting from N—H bends tend to be broader (due to hydrogen bonding) and more intense (due to being more polar) than those caused by C═C stretches, and they will be accompanied by N—H stretches at 3500−3300 cm^{-1} (Figure 10.12).

The stretch of the C—H bond of an aldehyde group shows two absorption bands—one at ~2820 cm^{-1} and the other at ~2720 cm^{-1} (Figure 10.16). This makes aldehydes relatively easy to identify because essentially no other absorption occurs at these wavenumbers.

▲ Figure 10.16

The absorptions at ~2820 cm^{-1} and ~2720 cm^{-1} readily identify an aldehyde group. Note also the intense absorption band at ~1730 cm^{-1} indicating a C═O bond.

10.14 THE ABSENCE OF ABSORPTION BANDS

The absence of an absorption band can be as useful as the presence of one in identifying a compound by IR spectroscopy.

For example, the spectrum in Figure 10.17 shows a strong absorption at ~1100 cm^{-1}, indicating the presence of a C—O bond. Clearly, the compound is not an alcohol because there is no absorption above 3100 cm^{-1}. Nor is it a carbonyl compound because there is no absorption at ~1700 cm^{-1}. The compound has no C≡C, C═C, C≡N, or C═N

bonds. We may deduce, then, that the compound is an ether. Its C—H absorption bands show that it has hydrogens only on sp^3 carbons (2950 cm^{-1}). The compound is in fact diethyl ether.

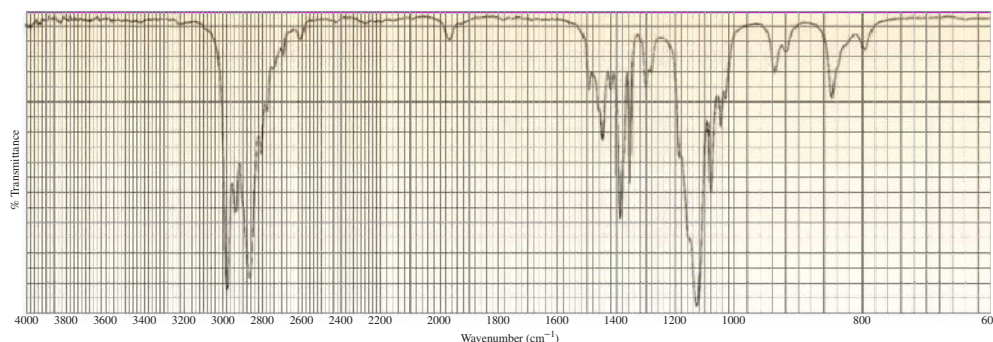



Figure 10.17
The IR spectrum of diethyl ether.

PROBLEM 21♦

A nitrogen-containing compound shows no absorption band at ~3400 cm^{-1} and no absorption bands between ~1700 cm^{-1} and ~1600 cm^{-1}. What class of compound is it?

PROBLEM 22

How could IR spectroscopy be used to distinguish between the following compounds?

a. a ketone and an aldehyde
b. benzene and cyclohexene
c. cyclohexene and cyclohexane
d. a primary amine and a tertiary amine

10.15 HOW TO INTERPRET AN INFRARED SPECTRUM

We will now look at some IR spectra and see what we can deduce about the structures of the compounds that give rise to the spectra. We might not be able to identify the compound precisely, but when we are told what it is, its structure should fit our observations.

Compound 1. The absorptions in the 3000 cm^{-1} region in Figure 10.18 indicate that hydrogens are attached to sp^2 carbons (3050 cm^{-1}) but not to sp^3 carbons. The sharp absorptions at 1600 cm^{-1} and 1460 cm^{-1} indicate that the compound has a benzene ring. The absorptions at 2810 cm^{-1} and 2730 cm^{-1} show that the compound is an aldehyde. The characteristically strong absorption band for the carbonyl group (C═O) is lower (~1700 cm^{-1}) than normal (1720 cm^{-1}), so the carbonyl group has partial single-bond character. Thus, it must be attached directly to the benzene ring, so electron delocalization from the ring can reduce the double bond character of the carbonyl group. The compound is benzaldehyde.

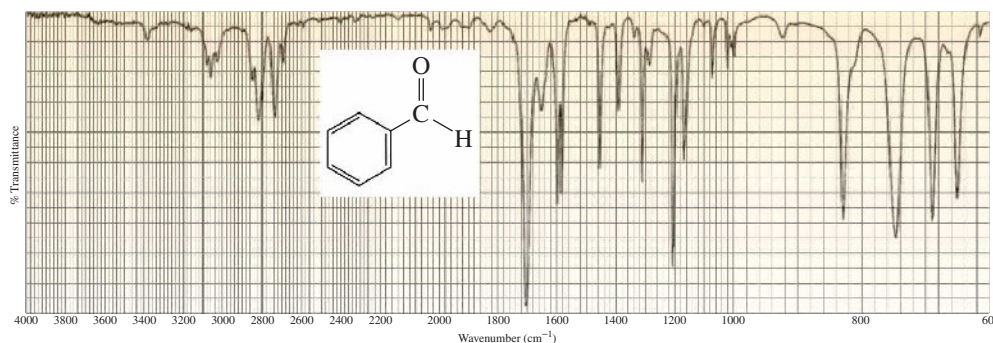
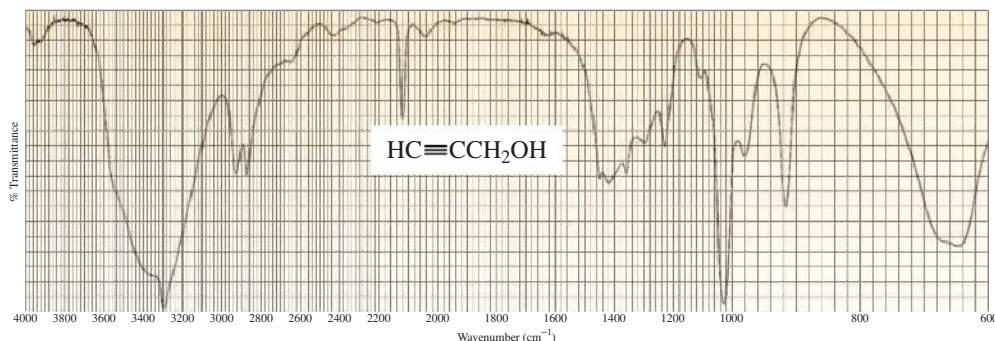



Figure 10.18
The IR spectrum of Compound 1.

Compound 2. The absorptions in the 3000 cm^{-1} region in Figure 10.19 indicate that hydrogens are attached to sp^3 carbons (2950 cm^{-1}) but not to sp^2 carbons. The shape of the strong absorption band at 3300 cm^{-1} is characteristic of an O—H group of an alcohol. The absorption at 2100 cm^{-1} indicates that the compound has a triple bond. The sharp absorption band at 3300 cm^{-1} indicates that the compound has a hydrogen attached to an *sp* carbon, so we know it is a terminal alkyne. The structure of the compound is shown on the spectrum.

◀ **Figure 10.19**
The IR spectrum of Compound 2.

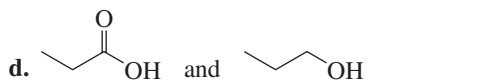
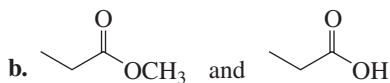
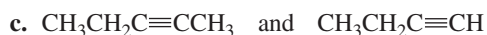
PROBLEM 23

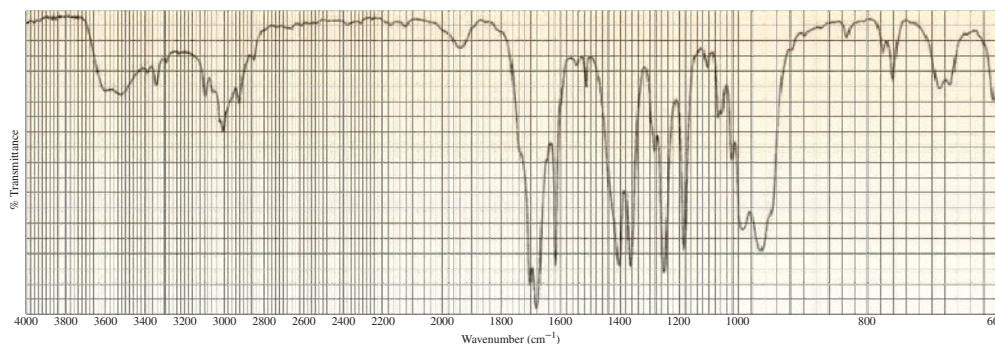
For each of the following pairs of compounds, name one absorption band that could be used to distinguish between them.

a. CH_3CH_2OH and $CH_3CH_2NH_2$

b. $CH_3CH_2C(=O)OCH_3$ and $CH_3CH_2C(=O)OH$

c. $CH_3CH_2C{\equiv}CCH_3$ and $CH_3CH_2C{\equiv}CH$

d. $CH_3CH_2C(=O)OH$ and $CH_3CH_2CH_2OH$

PROBLEM 24♦

Identify the compound with molecular formula C_4H_6O that gives the infrared spectrum shown here.

10.16 ULTRAVIOLET AND VISIBLE SPECTROSCOPY

Ultraviolet and visible (UV/Vis) spectroscopy provides information about compounds that have conjugated double bonds. If a molecule absorbs **ultraviolet light,** a UV spectrum is obtained; if it absorbs **visible light,** a visible spectrum is obtained. *Ultraviolet light* has wavelengths ranging from 180 to 400 nm (nanometers); *visible light* has wavelengths ranging from 400 to 780 nm.

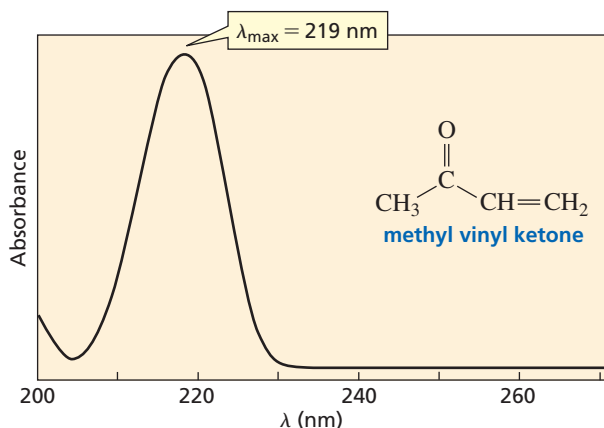
$$E = \frac{hc}{\lambda}$$

Wavelength (λ) is inversely related to the energy of the radiation, so the shorter the wavelength, the greater the energy of the radiation. Ultraviolet light, therefore, has greater energy than visible light.

The shorter the wavelength, the greater the energy of the radiation.

The UV spectrum of methyl vinyl ketone is shown in Figure 10.20. The λ_{max} (stated as "lambda max") is the wavelength at which the absorption band has its maximum absorbance. For methyl vinyl ketone, $\lambda_{max} = 219$ nm.

Only compounds with π electrons can produce ultraviolet and visible spectra.

▶ **Figure 10.20**
The UV spectrum of methyl vinyl ketone.

Ultraviolet Light and Sunscreens

Exposure to ultraviolet (UV) light stimulates specialized cells in the skin to produce a black pigment known as melanin, which causes the skin to look tan. Melanin absorbs UV light, so it protects our bodies from the harmful effects of the sun. If more UV light reaches the skin than melanin can absorb, the light will "burn" the skin and cause the reactions that can result in skin cancer.

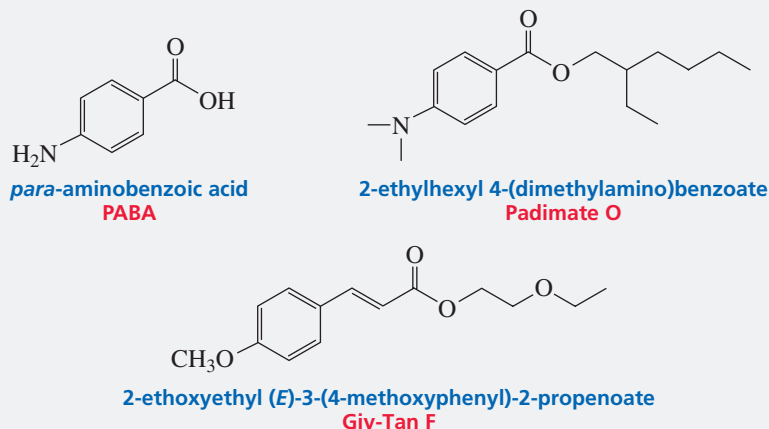
UV-A is the lowest-energy UV light (315 to 400 nm). It is the light that causes skin to wrinkle. Much of the more dangerous, higher-energy light—namely, UV-B (290 to 315 nm) and UV-C (180 to 290 nm)—is filtered out by the ozone layer in the stratosphere, which is why the thinning of the ozone layer has become such an important issue (Section 14.8).

Applying a sunscreen can protect skin from UV light. The amount of protection from UV-B light (the light that causes skin to burn) is indicated by the sunscreen's SPF (sun protection factor); the higher the SPF, the greater the protection. Some sunscreens contain an inorganic component, such as zinc oxide, which reflects the light as it reaches the skin. Others contain a compound that absorbs UV light.

para-Aminobenzoic acid (PABA) was the first commercially available UV-absorbing sunscreen. It absorbs UV-B light, but is not very soluble in oily skin lotions. Thus, the next generation of sunscreens contained Padimate O, a less polar compound. Subsequent research showed that sunscreens need to absorb both UV-B and UV-A light in order to give the best protection against skin cancer. Now the FDA requires that sunscreens, such as Giv-Tan F, protect against both UV-A and UV-B light.

H_2N–C$_6$H$_4$–COOH
para-aminobenzoic acid
PABA

2-ethylhexyl 4-(dimethylamino)benzoate
Padimate O

CH_3O–C$_6$H$_4$–CH=CH–COO–CH$_2$CH$_2$–O–CH$_2$CH$_3$
2-ethoxyethyl (*E*)-3-(4-methoxyphenyl)-2-propenoate
Giv-Tan F

10.17 THE EFFECT OF CONJUGATION ON λ_{max}

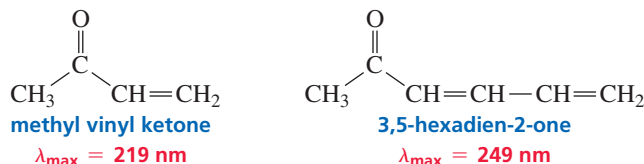
The more conjugated double bonds a compound has, the longer is the wavelength at which the λ_{max} occurs. For example, the λ_{max} for 3,5-hexadien-2-one is at a longer wavelength (249 nm) than the λ_{max} for methyl vinyl ketone (219 nm) because 3,5-hexadien-2-one has three conjugated double bonds, whereas methyl vinyl ketone has two double bonds.

The λ_{max} increases as the number of conjugated double bonds increases.

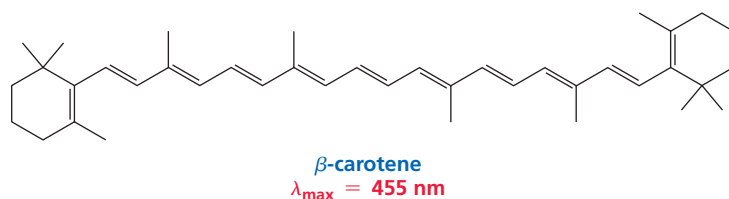
$CH_3C(=O)CH{=}CH_2$
methyl vinyl ketone
λ_{max} = 219 nm

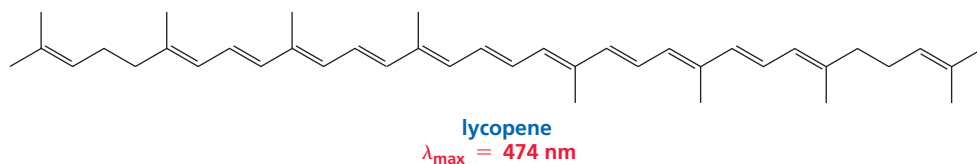
$CH_3C(=O)CH{=}CH{-}CH{=}CH_2$
3,5-hexadien-2-one
λ_{max} = 249 nm

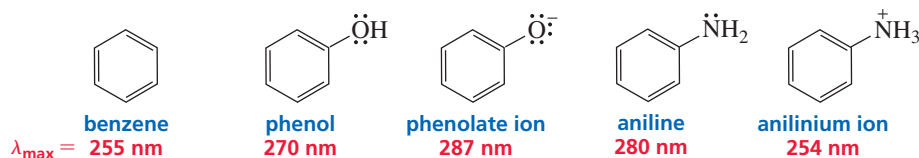
Table 10.4 Values of λ_{max} for Ethylene and Conjugated Polyenes

Compound	λ_{max} (nm)
$H_2C{=}CH_2$	165
(diene)	217
(triene)	256
(tetraene)	290
(pentaene)	334
(hexaene)	364

The λ_{max} values for several conjugated polyenes are listed in Table 10.4. Thus, the λ_{max} of a compound can be used to estimate the number of conjugated double bonds in a compound.

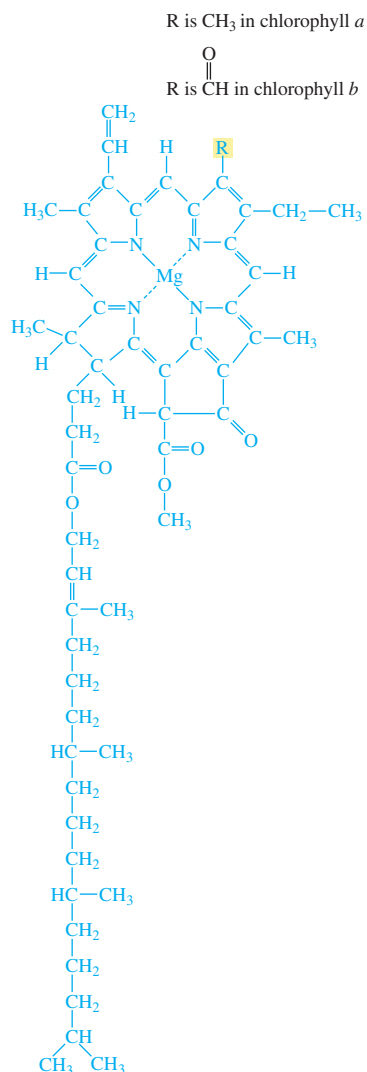
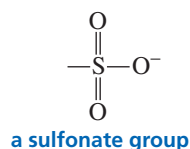
If a compound has enough conjugated double bonds, it will absorb visible light (light with wavelengths > 400 nm) and the compound will be colored. For example, β-carotene, a precursor of vitamin A with a λ_{max} = 455 nm, is an orange substance found in carrots, apricots, and the feathers of flamingos.

β-carotene
λ_{max} = 455 nm

Lycopene, with a λ_{max} = 474 nm—found in tomatoes, watermelon, and pink grapefruit—is red.

lycopene
λ_{max} = 474 nm

The lone-pair electrons on oxygen and nitrogen in the compounds shown here are available to interact by resonance (electron delocalization) with the π electron cloud of the benzene ring; such an interaction increases the λ_{max}.

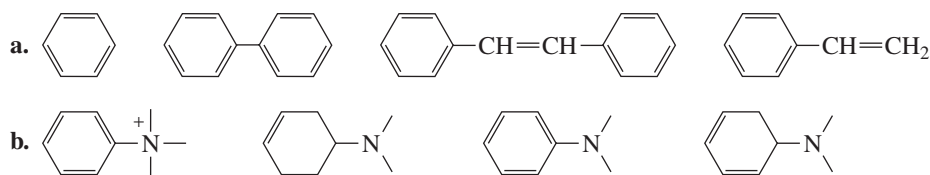
	benzene	phenol	phenolate ion	aniline	anilinium ion
λ_{max} =	255 nm	270 nm	287 nm	280 nm	254 nm

Removing a proton from phenol increases the λ_{max} because the phenolate ion has an additional lone pair. Protonating aniline decreases the λ_{max} because the lone pair is no longer available to interact with the π cloud of the benzene ring. Because the anilinium ion does not have a lone pair, its λ_{max} is similar to that of benzene.

R is CH_3 in chlorophyll *a*

R is CH (with =O) in chlorophyll *b*

Chlorophyll *a* and *b* are highly conjugated compounds that absorb visible light, causing green light to be reflected from the surface tissues of plants.

PROBLEM 25♦

Rank each set of compounds in order of decreasing λ_{max}:

a. benzene; biphenyl; $C_6H_5-CH=CH-C_6H_5$; $C_6H_5-CH=CH_2$

b. $C_6H_5-\overset{+}{N}(CH_3)_3$; cyclohexenyl$-N(CH_3)_2$; cyclohexadienyl$-N(CH_3)_2$; cyclohexadienyl$-N(CH_3)_2$

10.18 THE VISIBLE SPECTRUM AND COLOR

White light is a mixture of all visible wavelengths. If any of these wavelengths are removed from white light, the eye registers the remaining light as colored. Therefore, any compound that absorbs visible light appears colored. The perceived color depends on the precise wavelengths reaching the eye. The wavelengths that the compound does *not* absorb are reflected back to the viewer, producing the color the viewer sees.

The relationship between the wavelengths of the light that a substance absorbs and the substance's observed color is shown in Table 10.5. Notice that two absorption bands are necessary to produce green. Most colored compounds have fairly broad absorption bands, but vivid colors have narrow absorption bands. The human eye is able to distinguish more than a million different shades of color!

Table 10.5 Dependence of the Color Observed on the Wavelength of Light Absorbed

Wavelengths absorbed (nm)	Color absorbed	Color observed
380–460	blue-violet	yellow
380–500	blue	orange
440–560	blue-green	red
480–610	green	purple
540–650	orange	blue
380–420 and 610–700	purple	green

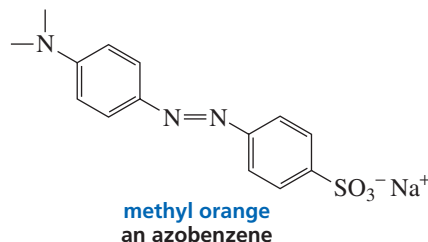
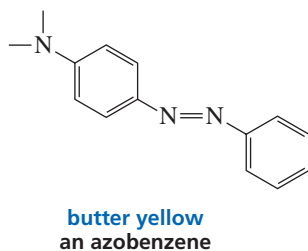
Azobenzenes (benzene rings connected by an N=N bond) have an extended conjugated system that causes them to absorb visible light. The two shown here are used commercially as dyes. Changing the number of conjugated double bonds and the substituents attached to them creates a large number of different colors. Notice that the only difference between butter yellow and methyl orange is an SO_3^- group.

$-\overset{O}{\underset{O}{S}}-O^-$

a sulfonate group

butter yellow
an azobenzene

$SO_3^-\ Na^+$

methyl orange
an azobenzene

When margarine was first produced, it was colored with butter yellow to make it look more like butter. (White margarine would not be very appetizing.) This dye was abandoned after it was found to be carcinogenic. β-Carotene (page 389) is now used to color margarine.

What Makes Blueberries Blue and Strawberries Red?

A class of highly conjugated compounds called *anthocyanins* is responsible for the red, purple, and blue colors of many flowers (poppies, peonies, cornflowers), fruits (cranberries, rhubarb, strawberries, blueberries, the red skin of apples, the purple skin of grapes), and vegetables (beets, radishes, red cabbage).

In a neutral or basic solution, the monocyclic fragment (on the right-hand side of the anthocyanin) is not conjugated with the rest of the molecule, so the anthocyanin does not absorb visible light and is, therefore, a colorless compound. In an acidic environment, however, the OH group becomes protonated and water is eliminated. (Recall that water, being a weak base, is a good leaving group; see Section 9.2). Loss of water results in the third ring becoming conjugated with the rest of the molecule.

monocyclic fragment

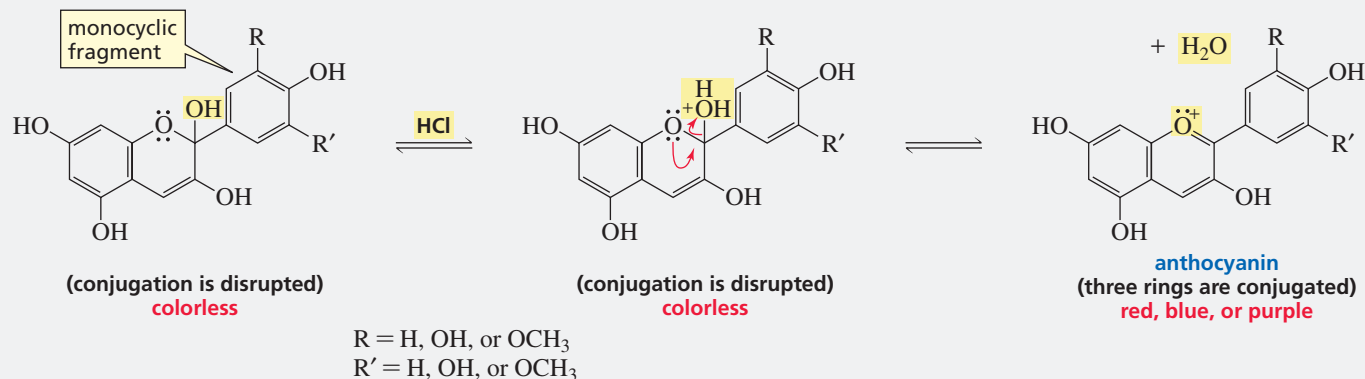
HCl

$+ H_2O$

(conjugation is disrupted)
colorless

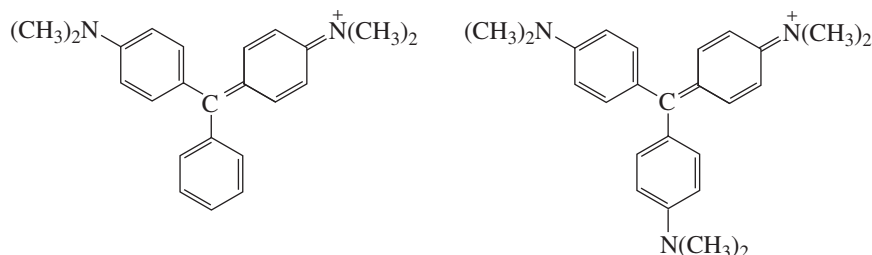
(conjugation is disrupted)
colorless

anthocyanin
(three rings are conjugated)
red, blue, or purple

$R = H, OH, or OCH_3$
$R' = H, OH, or OCH_3$

As a result of the increase in conjugation, the anthocyanin absorbs visible light with wavelengths between 480 and 550 nm. The exact wavelength of light absorbed depends on the substituents (R and R′) on the anthocyanin. Thus, the flower, fruit, or vegetable appears red, purple, or blue, depending on what R and R′ are. You can see this color change if you alter the pH of cranberry juice so that it is no longer acidic.

PROBLEM 26♦

a. At pH = 7, one of the ions shown here is purple and the other is blue. Which is which?
b. What would be the difference in the colors of the compounds at pH = 3?

$(CH_3)_2N$ … $\overset{+}{N}(CH_3)_2$ $(CH_3)_2N$ … $\overset{+}{N}(CH_3)_2$ … $N(CH_3)_2$

PROBLEM 27♦

Predict from Table 10.5 the two colors that, when mixed together, produce green.

Lycopene, β-carotene, and anthocyanins are found in the leaves of trees, but their characteristic colors are usually obscured by the green color of chlorophyll. Chlorophyll is an unstable molecule, so plants must continually synthesize it. Its synthesis requires sunlight and warm temperatures. As the weather becomes colder in the fall, plants can no longer replace chlorophyll as it degrades, so the other colors become apparent.

10.19 SOME USES OF UV/VIS SPECTROSCOPY

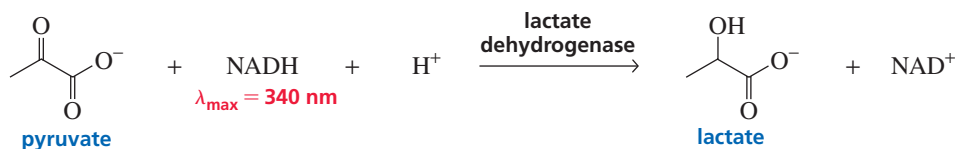
UV/Vis spectroscopy is not nearly as useful as other instrumental techniques for determining the structures of organic compounds. However, UV/Vis spectroscopy has many other important uses. A few are described here.

UV/Vis spectroscopy is often used to measure reaction rates. The rate of any reaction can be measured, as long as one of the reactants or one of the products absorbs UV or visible light at a wavelength at which the other reactants and products have little or no absorbance.

For example, the enzyme lactate dehydrogenase catalyzes the reduction of pyruvate to lactate by NADH (Section 19.6). NADH is the only species in the reaction mixture that

▲ **Figure 10.21**
The rate of reduction of pyruvate by NADH is measured by monitoring the decrease in absorbance at 340 nm.

absorbs light at 340 nm, so the rate of the reaction can be determined by monitoring the decrease in absorbance at 340 nm (Figure 10.21).

pyruvate + NADH (λ_{max} = 340 nm) + H^+ $\xrightarrow{\text{lactate dehydrogenase}}$ lactate + NAD^+

PROBLEM 28♦

Describe a way to determine the rate of the alcohol dehydrogenase-catalyzed oxidation of ethanol by NAD^+.

The pK_a of a compound can be determined by UV/Vis spectroscopy if either the acidic form or the basic form of the compound absorbs UV or visible light. For example, the phenolate ion has a λ_{max} at 287 nm. If the absorbance at 287 nm is monitored as a function of pH, the pK_a of phenol can be ascertained by determining the pH at which exactly one-half the increase in absorbance has occurred (Figure 10.22). At this pH, half of the phenol has been converted into phenolate ion, so this pH is equal to the pK_a of the compound.

▲ **Figure 10.22**
The absorbance of an aqueous solution of phenol as a function of pH.

Recall that the pK_a of a compound is the pH at which half the compound exists in its acidic form and half exists in its basic form (Section 2.10).

PROBLEM 29♦

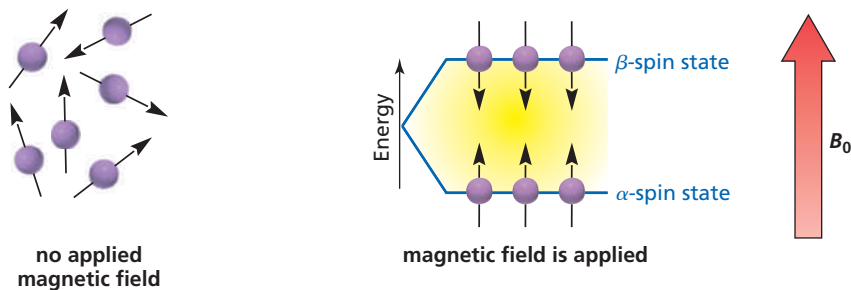
The absorbance of a solution of a weak acid was measured under the same conditions at a series of pH values. Its conjugate base is the only species in the solution that absorbs UV light at the wavelength used. Estimate the pK_a of the acid from the data obtained.

pH	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0
Absorbance	0	0	0.10	0.50	0.80	1.10	1.50	1.60	1.60	1.60

10.20 AN INTRODUCTION TO NMR SPECTROSCOPY

Nuclei that have an odd number of protons or an odd number of neutrons (or both) have a property called spin that allows them to be studied by NMR (^1H, ^{13}C, ^{15}N, ^{19}F, and ^{31}P). Nuclei such as ^{12}C and ^{16}O do not have spin and, therefore, cannot be studied by NMR. Because hydrogen nuclei (protons) were the first nuclei studied by **nuclear magnetic resonance (NMR),** the acronym *NMR* is generally assumed to mean **^{1}H NMR (proton magnetic resonance).**

As a result of its charge, a nucleus with spin has a magnetic moment and generates a magnetic field similar to the magnetic field generated by a small bar magnet. In the absence of an applied magnetic field, the magnetic moments of the nuclei are randomly oriented. However, when placed between the poles of a strong magnet, the magnetic moments of the nuclei align either *with* or *against* the applied magnetic field (Figure 10.23).

There are additional spectroscopy problems in the *Study Guide and Solutions Manual.*

▲ **Figure 10.23**
In the absence of an applied magnetic field, the magnetic moments of the nuclei are randomly oriented. In the presence of an applied magnetic field, the magnetic moments of the nuclei line up with (the α-spin state) or against (the β-spin state) the applied magnetic field.

Nuclei with magnetic moments that align with the field are in the lower-energy ***α*-spin state,** whereas those with magnetic moments that align against the field are in the higher-energy ***β*-spin state.** The β-spin state is higher in energy because more energy is needed to align the magnetic moments against the field than with it.

The energy difference (ΔE) between the α- and β-spin states depends on the strength of the **applied magnetic field** (B_0): the greater the strength of the applied magnetic field, the greater the ΔE (Figure 10.24).

When a sample is subjected to a pulse of radiation whose energy corresponds to the difference in energy (ΔE) between the α- and β-spin states, nuclei in the α-spin state are promoted to the β-spin state. This transition is called "flipping" the spin.

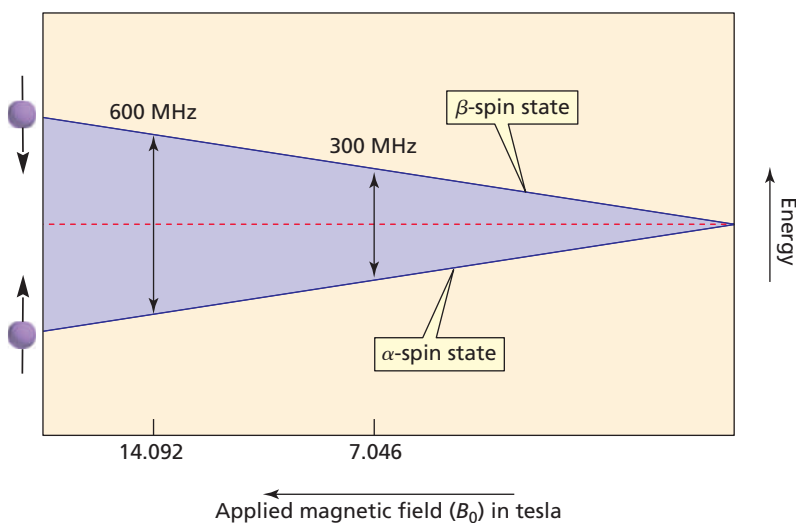
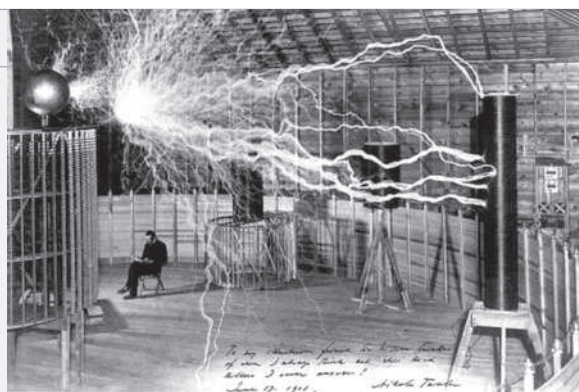



Figure 10.24
The difference in energy between the α- and β-spin states increases as the strength of the applied magnetic field increases.

When the nuclei absorb radiation and flip their spins, they generate signals whose frequency depends on the difference in energy (ΔE) between the α- and β-spin states. The NMR spectrometer detects these signals and plots their frequency versus their intensity; this plot is an NMR spectrum (see Figure 10.26 in page 396).

Nikola Tesla (1856–1943)

The tesla, used to measure the strength of a magnetic field, was named in honor of Nikola Tesla. Tesla was born in Croatia, emigrated to the United States in 1884, and became a citizen in 1891. He was a proponent of the use of alternating current to distribute electricity and bitterly fought Thomas Edison, who promoted direct current. Tesla was granted a patent for developing the radio in 1900, but Guglielmo Marconi was also given a patent for its development in 1904. Not until 1943—a few months after his death—was Tesla's patent upheld by the U.S. Supreme Court.

Tesla held over 800 patents and is given credit for developing neon and fluorescent lighting, the electron microscope, the refrigerator motor, and the Tesla coil (a type of transformer for changing the voltage of alternating current). Perhaps his most important contribution was polyphase electric power, which became the prototype for all large power systems. He made most of his equipment himself, including insulators, a technology that was kept classified until recently because the same technology was being used for part of the U.S. Strategic Defense Initiative. Telsa frequently staged flamboyant high-voltage demonstrations, which may explain why he did not receive proper recognition for his work.

Nikola Tesla in his laboratory

10.21 SHIELDING CAUSES DIFFERENT HYDROGENS TO SHOW SIGNALS AT DIFFERENT FREQUENCIES

Because the frequency of an NMR signal depends on the strength of the magnetic field experienced by the nucleus (Figure 10.24), if all the hydrogens in a compound were to experience the same magnetic field, they would all give signals of the same frequency. If this were the case, all NMR spectra would consist of one signal, which would tell us nothing about the structure of the compound, except that it contains hydrogens.

A nucleus, however, is embedded in a cloud of electrons that partly *shields* it from the applied magnetic field. Fortunately for chemists, the **shielding** varies for different hydrogens in a molecule. In other words, all the hydrogens do not experience the same magnetic field.

What causes shielding? In a magnetic field, the electrons circulate about the nuclei and induce a local magnetic field that acts in opposition to the applied magnetic field and, therefore, subtracts from it. As a result, the **effective magnetic field**—the amount of magnetic field that the nuclei actually "sense" through the surrounding electrons—is somewhat smaller than the applied magnetic field:

The electron density of the environment in which the proton is located shields the proton from the applied magnetic field.

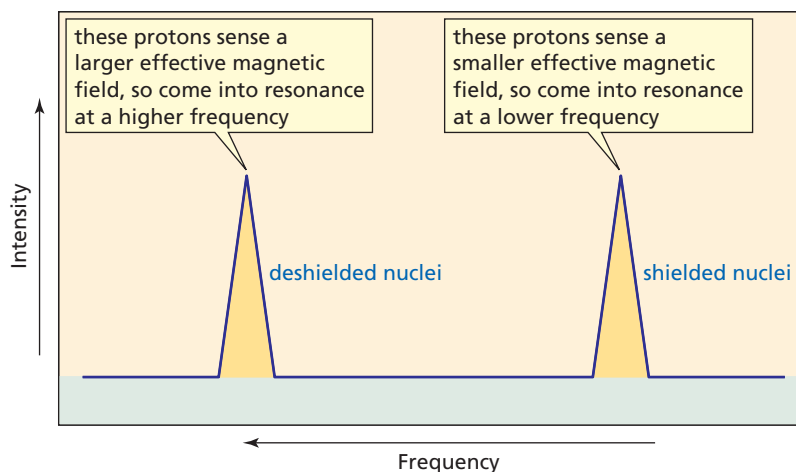
$$B_{\text{effective}} = B_{\text{applied}} - B_{\text{local}}$$

This means that the greater the electron density of the environment in which the proton* is located, the more the proton is shielded from the applied magnetic field, the greater is B_{local}, and the smaller is $B_{\text{effective}}$.

The larger the magnetic field sensed by the proton, the higher the frequency of the signal.

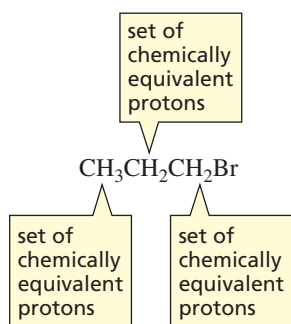
Thus, protons in electron-rich environments sense a *smaller effective magnetic field*. Therefore, they require a *lower frequency* to come into resonance—that is, flip their spin—because ΔE is smaller (Figure 10.24). Protons in electron-poor environments sense a *larger effective magnetic field* and so require a *higher frequency* to come into resonance—that is, flip their spins—because ΔE is larger.

An NMR spectrum exhibits a signal for each proton in a different environment. Protons in electron-rich environments are more shielded and appear at lower frequencies (on the right-hand side of the spectrum; Figure 10.25). Protons in electron-poor environments are less shielded and appear at higher frequencies (on the left-hand side of the spectrum). Notice that high frequency in an NMR spectrum is on the left-hand side, just as it is in IR and UV/Vis spectra.

deshielded = less shielded

▶ Figure 10.25
Shielded protons come into resonance at lower frequencies than deshielded nuclei.

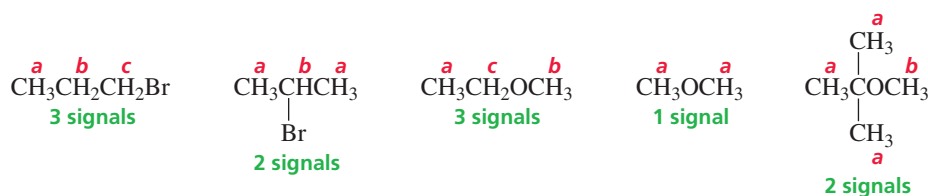
*In discussions of NMR spectroscopy, the terms *proton* and *hydrogen* are both used to describe a covalently bonded hydrogen.

10.22 THE NUMBER OF SIGNALS IN AN ^{1}H NMR SPECTRUM

Protons in the same environment are called **chemically equivalent protons.** For example, 1-bromopropane has three different sets of chemically equivalent protons: the three methyl protons are chemically equivalent because of rotation about the C—C bond; the two methylene (CH_2) protons on the middle carbon are chemically equivalent; and the two methylene protons on the carbon bonded to the bromine make up the third set of chemically equivalent protons.

Each set of chemically equivalent protons produces an NMR signal.

Each set of chemically equivalent protons in a compound produces a separate signal in its ^{1}H NMR spectrum. Thus, 1-bromopropane has three signals in its ^{1}H NMR spectrum because it has three sets of chemically equivalent protons. (Sometimes the signals are not sufficiently separated and overlap each other. When this happens, one sees fewer signals than anticipated.)

2-Bromopropane has two sets of chemically equivalent protons, so it has two signals in its ^{1}H NMR spectrum. The six methyl protons are equivalent so they produce only one signal, and the hydrogen bonded to the middle carbon gives the second signal.

$\overset{a}{CH_3}\overset{b}{CH_2}\overset{c}{CH_2}Br$	$\overset{a}{CH_3}\overset{b}{CH}(Br)\overset{a}{CH_3}$	$\overset{a}{CH_3}\overset{c}{CH_2}O\overset{b}{CH_3}$	$\overset{a}{CH_3}O\overset{a}{CH_3}$	$(\overset{a}{CH_3})_3CO\overset{b}{CH_3}$
3 signals	2 signals	3 signals	1 signal	2 signals

You can tell how many sets of chemically equivalent protons a compound has from the number of signals in its ^{1}H NMR spectrum.

Ethyl methyl ether has three sets of chemically equivalent protons: the methyl protons on the carbon adjacent to the oxygen, the methylene protons on the carbon adjacent to the oxygen, and the methyl protons on the carbon that is one carbon removed from the oxygen. The chemically equivalent protons in the compounds shown here are designated by the same letter.

PROBLEM 30

How many signals would you expect to see in the ^{1}H NMR spectrum of each of the five compounds with molecular formula C_6H_{14}?

PROBLEM 31♦

How many signals would you expect to see in the ^{1}H NMR spectrum of each of the following compounds?

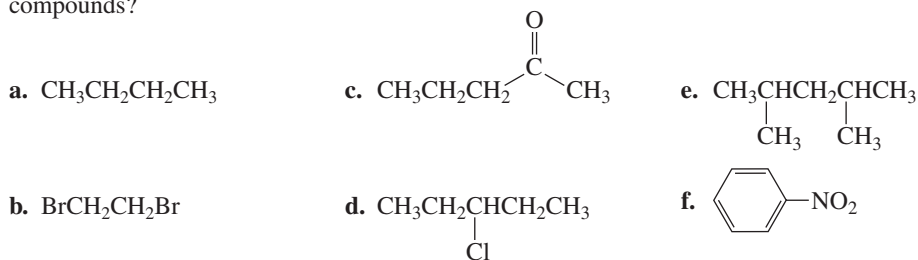
a. $CH_3CH_2CH_2CH_3$

b. $BrCH_2CH_2Br$

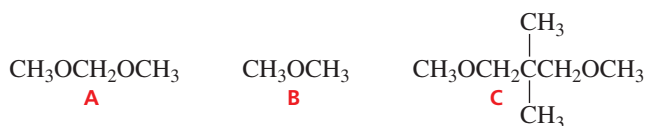
c. $CH_3CH_2CH_2C(=O)CH_3$

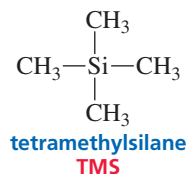
d. $CH_3CH_2CH(Cl)CH_2CH_3$

e. $CH_3CH(CH_3)CH_2CH(CH_3)CH_3$

f. C_6H_5—NO_2

PROBLEM 32

How could you distinguish the ^{1}H NMR spectra of the following compounds?

$CH_3OCH_2OCH_3$ **A** CH_3OCH_3 **B** $CH_3OCH_2C(CH_3)_2CH_2OCH_3$ **C**

10.23 THE CHEMICAL SHIFT TELLS HOW FAR THE SIGNAL IS FROM THE REFERENCE SIGNAL

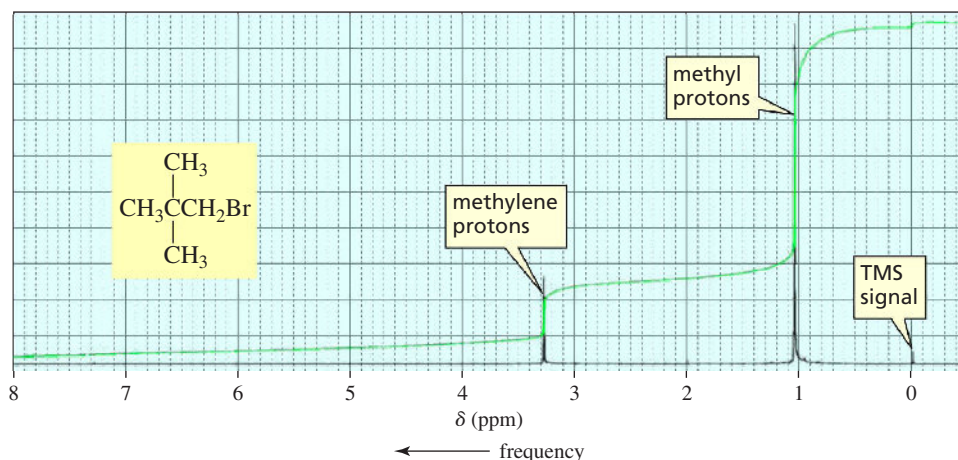
$(CH_3)_4Si$
tetramethylsilane
TMS

A small amount of an inert **reference compound** is added to the sample tube containing the compound whose NMR spectrum is to be taken. The most commonly used reference compound is tetramethylsilane (TMS).

The methyl protons of TMS are in a more electron-rich environment than are most protons in organic molecules because silicon is less electronegative than carbon (their electronegativities are 1.8 and 2.5, respectively). Consequently, the signal for the methyl protons of TMS is at a lower frequency than most other signals (that is, the TMS signal appears to the right of the other signals).

The position at which a signal occurs in an NMR spectrum is called the *chemical shift*. The **chemical shift** is a measure of how far the signal is from the signal for the reference compound. The most common scale for chemical shifts is the δ (delta) scale. The TMS signal defines the zero position on the δ scale (Figure 10.26).

Most proton chemical shifts are between 0 and 12 ppm.

Figure 10.26
The ^{1}H NMR spectrum of 1-bromo-2,2-dimethylpropane. The TMS signal is a reference signal from which chemical shifts are measured; it defines the zero position on the scale.

The greater the value of the chemical shift (δ), the higher the absorption frequency.

The ^{1}H NMR spectrum in Figure 10.26 shows that the chemical shift (δ) of the methyl protons is at 1.05 ppm and the chemical shift of the methylene protons, which are deshielded by the electron-withdrawing bromine, is at 3.28 ppm. *Notice that low-frequency (shielded) signals have small δ (ppm) values, whereas high-frequency (deshielded) signals have large δ values.*

The following diagram will help you keep track of the terms associated with NMR spectroscopy:

PROBLEM 33♦

Where would you expect to find the [1]H NMR signal of $(CH_3)_2Mg$ relative to the TMS signal? (*Hint:* Magnesium is less electronegative than silicon.)

10.24 THE RELATIVE POSITIONS OF [1]H NMR SIGNALS

Protons in electron-poor environments show signals at high frequencies.

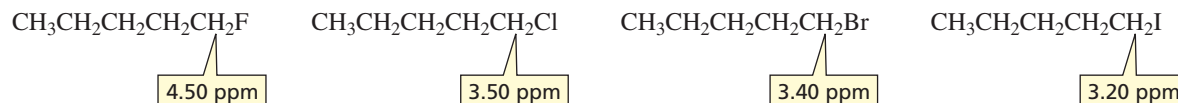
The [1]H NMR spectrum in Figure 10.26 has two signals because the compound has two different kinds of protons. The methylene protons are in a *less electron-rich environment* than are the methyl protons because the methylene protons are closer to the electron-withdrawing bromine. Therefore, the methylene protons are *less shielded* from the applied magnetic field. As a result, the signal for these protons occurs at a higher frequency than the signal for the more shielded methyl protons.

> *Remember that the right-hand side of an NMR spectrum is the low-frequency side, where protons in electron-rich environments (more shielded) show a signal. The left-hand side is the high-frequency side, where protons in electron-poor environments (less shielded) show a signal (Figure 10.25).*

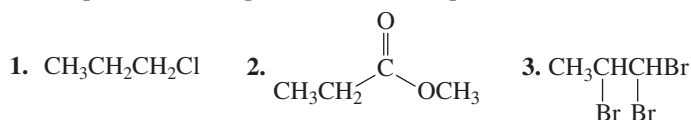
We expect the [1]H NMR spectrum of 1-nitropropane to have three signals because the compound has three different kinds of protons. The closer the protons are to the electron-withdrawing nitro group, the less they are shielded from the applied magnetic field, so the higher the frequency at which their signal will appear. Thus, the protons closest to the nitro group show a signal at the highest frequency (4.37 ppm), and the ones farthest from the nitro group show a signal at the lowest frequency (1.04 ppm).

Electron withdrawal causes NMR signals to appear at higher frequencies (at larger δ values).

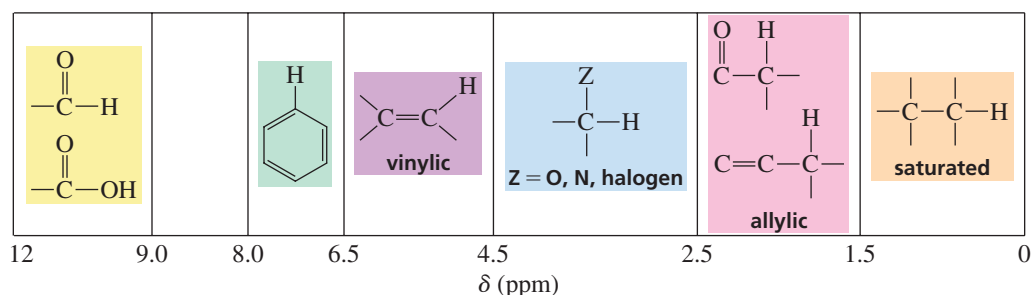
Compare the chemical shifts of the methylene protons immediately adjacent to the halogen in the following alkyl halides. The position of the signal depends on the electronegativity of the halogen—as the electronegativity of the halogen increases, the shielding of the protons decreases, so the frequency of the signal increases. Thus, the signal for the methylene protons adjacent to fluorine (the most electronegative of the halogens) occurs at the highest frequency, whereas the signal for the methylene protons adjacent to iodine (the least electronegative of the halogens) occurs at the lowest frequency.

$CH_3CH_2CH_2CH_2CH_2F$	$CH_3CH_2CH_2CH_2CH_2Cl$	$CH_3CH_2CH_2CH_2CH_2Br$	$CH_3CH_2CH_2CH_2CH_2I$
4.50 ppm	3.50 ppm	3.40 ppm	3.20 ppm

PROBLEM 34♦

a. Which proton or set of protons in each of the following compounds is the least shielded?
b. Which proton or set of protons in each compound is the most shielded?

1. $CH_3CH_2CH_2Cl$ **2.** $CH_3CH_2C(=O)OCH_3$ **3.** $CH_3CHBrCHBr$ (CH₃CH(Br)CH(Br))

10.25 THE CHARACTERISTIC VALUES OF CHEMICAL SHIFTS

Approximate values of chemical shifts for different kinds of protons are listed in Table 10.6.

An [1]H NMR spectrum can be divided into seven regions, one of which is empty. If you can remember the kinds of protons that appear in each region, you will be able to tell what kinds of protons a molecule has from a quick look at its NMR spectrum.

Carbon is more electronegative than hydrogen (Table 1.3 on page 37). Therefore, the chemical shift of a **methine proton** (a hydrogen bonded to an sp^3 carbon that is attached to *three* carbons) is more deshielded and so shows a chemical shift at a higher frequency than the chemical shift of **methylene protons** (hydrogens bonded to an sp^3 carbon that is attached to *two* carbons) in a similar environment. Likewise, the chemical shift of methylene protons is at a higher frequency than the chemical shift of **methyl protons** (hydrogens bonded to an sp^3 carbon that is attached to *one* carbon) in a similar environment (Table 10.6).

—CH— **methine**

—CH_2— **methylene**

—CH_3 **methyl**

methine proton: C_3C—H, **1.55 ppm**

methylene proton: C_2CH—H, **1.20 ppm**

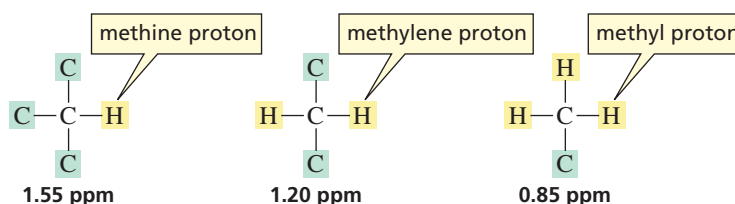
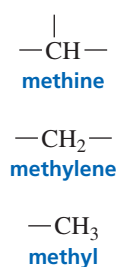
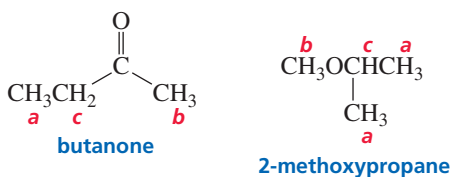
methyl proton: CH_2C—H, **0.85 ppm**

For example, the ^1H NMR spectrum of butanone shows three signals. The signal at the lowest frequency is the signal for the ***a*** protons; these protons are farthest from the electron-withdrawing carbonyl group. The ***b*** and ***c*** protons are the same distance from the carbonyl group, but the signal for the ***c*** proton is at a higher frequency than the signal for the ***b*** protons because methylene protons appear at a higher frequency than do methyl protons in a similar environment.

Table 10.6 Approximate Values of Chemical Shifts (ppm) for ^1H NMR[a]

Type of proton	ppm	Type of proton	ppm	Type of proton	ppm	Type of proton	ppm
—CH_3	0.85	C_6H_5—CH_3	2.3	I—C—H	2.5–4	R—OH	Variable, 2–5
—CH_2—	1.20	—C≡C—H	2.4	Br—C—H	2.5–4	C_6H_5—OH	Variable, 4–7
—CH—	1.55	R—O—CH_3	3.3	Cl—C—H	3–4	C_6H_5—H	6.5–8
—C=C—CH_3	1.7	R—C(R)=CH_2	4.7	F—C—H	4–4.5	—C(=O)—H	9.0–10
—C(=O)—CH_3	2.1	R—C(R)=C(R)—H	5.3	R—NH_2	Variable, 1.5–4	—C(=O)—OH	Variable, 10–12
						—C(=O)—NH_2	Variable, 5–8

[a]The values are approximate because they are affected by neighboring substituents.

$CH_3CH_2C(=O)CH_3$ (a, c, b)
butanone

$CH_3OCH(CH_3)CH_3$ (b, c, a, a)
2-methoxypropane

In a similar environment, the signal for a methine proton occurs at a higher frequency than the signal for methylene protons, which occurs, in turn, at a higher frequency than the signal for methyl protons.

(In correlating an NMR spectrum with a structure, the set of protons responsible for the signal at the lowest frequency will be labeled ***a,*** the next set will be labeled ***b,*** the next set ***c,*** and so on.)

The signal for the ***a*** protons of 2-methoxypropane is the one at the lowest frequency because these protons are farthest from the electron-withdrawing oxygen. The ***b*** and ***c*** protons are the same distance from the oxygen, but the signal for the ***c*** proton appears at a higher frequency because, in a similar environment, a methine proton appears at a higher frequency than do methyl protons.

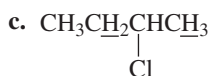
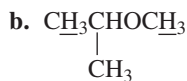
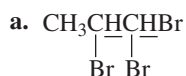
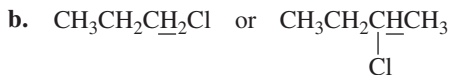
PROBLEM 35♦

Which of the underlined protons (or sets of protons) has the greater chemical shift (that is, the higher-frequency signal)?

a. $CH_3\underline{CH}(Br)\underline{CH}(Br)Br$ **b.** $C\underline{H_3}CH(CH_3)OC\underline{H_3}$ **c.** $CH_3C\underline{H_2}CH(Cl)C\underline{H_3}$

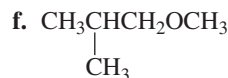
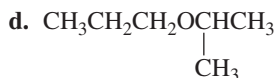
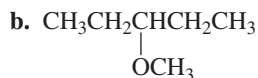
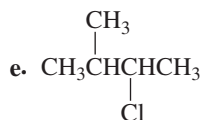
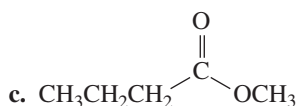
PROBLEM 36♦

Which of the underlined protons (or sets of protons) has the greater chemical shift (that is, the higher-frequency signal)?

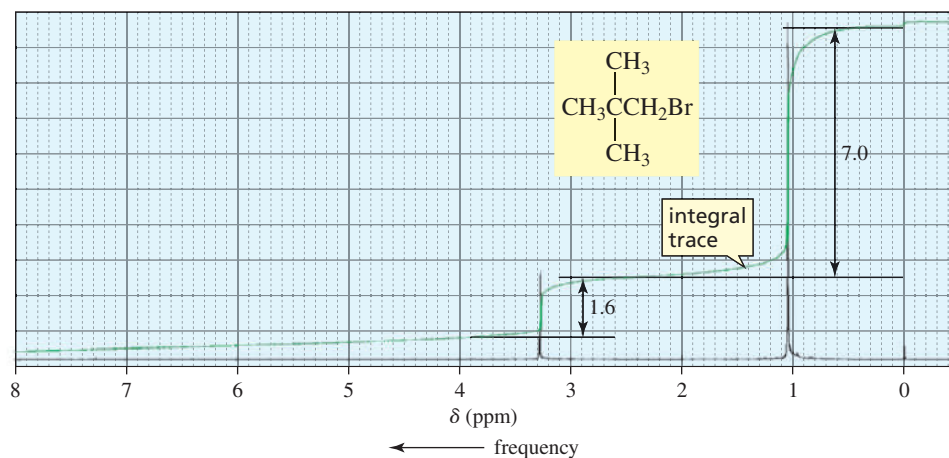
a. $CH_3CH_2\underline{CH_2}Cl$ or $CH_3CH_2\underline{CH_2}Br$ **b.** $CH_3CH_2\underline{CH_2}Cl$ or $CH_3CH_2\underline{CH}(Cl)CH_3$

PROBLEM 37

Without referring to Table 10.6, label the proton or set of protons in each compound that gives the signal at the lowest frequency ***a,*** at the next lowest ***b,*** and so on.

a. $CH_3CH_2CH_2C(=O)CH_3$ **c.** $CH_3CH_2CH_2C(=O)OCH_3$ **e.** $CH_3CH(CH_3)CH(Cl)CH_3$

b. $CH_3CH_2CH(OCH_3)CH_2CH_3$ **d.** $CH_3CH_2CH_2OCH(CH_3)CH_3$ **f.** $CH_3CH(CH_3)CH_2OCH_3$

10.26 THE INTEGRATION OF NMR SIGNALS REVEALS THE RELATIVE NUMBER OF PROTONS CAUSING EACH SIGNAL

The two signals in the ^1H NMR spectrum in Figure 10.27 are not the same size because *the area under each signal is proportional to the number of protons producing the signal*. The area under the signal occurring at the lower frequency is larger because the signal is produced by *nine* methyl protons, whereas the smaller, higher-frequency signal is produced by *two* methylene protons.

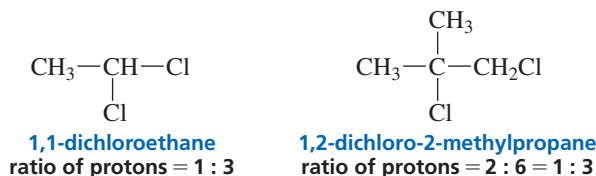
The area under each signal can be determined by an integral. An NMR spectrometer is equipped with a computer that calculates the integrals electronically and then displays them as an integral trace superimposed on the original spectrum (Figure 10.27). The

▲ **Figure 10.27**
Analysis of the integration line in the ^{1}H NMR spectrum of 1-bromo-2,2-dimethylpropane. The peak at 3.3 ppm has a smaller integral trace than the peak at 1.0 ppm because the peak at 3.3 ppm is produced by two methylene protons, whereas the peak at 1.0 ppm is produced by nine methyl protons.

height of each step in the integral trace is proportional to the area under the corresponding signal, which, in turn, is proportional to the number of protons producing the signal.

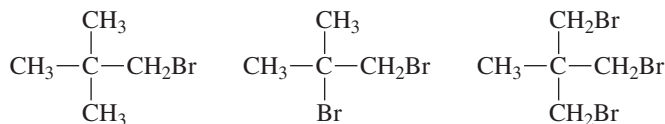
For example, the heights of the integration steps in Figure 10.27 tell us that the ratio of the integrals is approximately 1.6 : 7.0. Dividing by the smallest number gives a new ratio (1 : 4.4). We then need to multiply this ratio by a number that will make all the numbers in the ratio close to whole numbers—in this case, we multiply by 2. This means that the ratio of protons in the compound is 2 : 8.8, which is rounded to 2 : 9, since there can be only whole numbers of protons. (The measured integrals are approximate because of experimental error.) Modern spectrometers print the integrals as numbers on the spectrum; see Figure 10.28 on page 401.

Integration tells us the *relative* number of protons that produce each signal, not the *absolute* number. In other words, integration could not distinguish between the following two compounds because both would show an integral ratio of 1 : 3.

$CH_3-CH(Cl)-Cl$
1,1-dichloroethane
ratio of protons = 1 : 3

$CH_3-C(CH_3)(Cl)-CH_2Cl$
1,2-dichloro-2-methylpropane
ratio of protons = 2 : 6 = 1 : 3

PROBLEM 38♦

How would integration distinguish the ^{1}H NMR spectra of the following compounds?

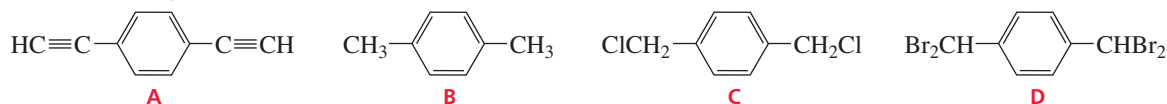
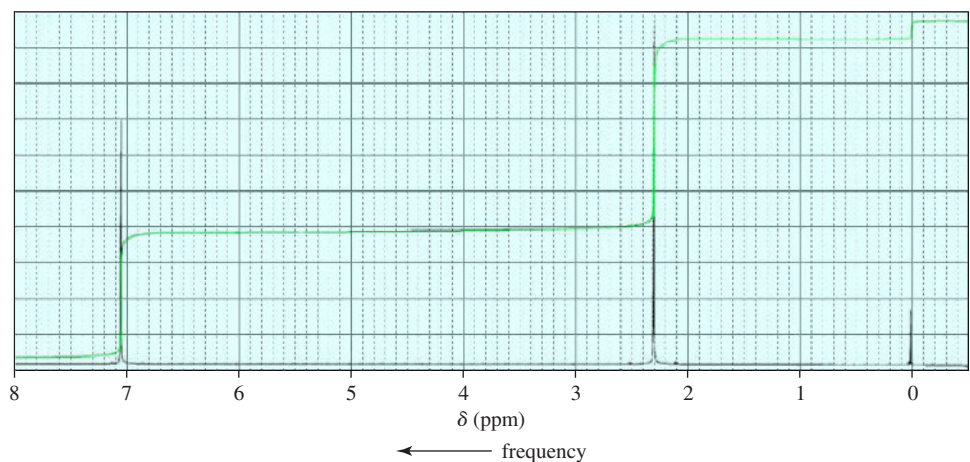
$CH_3-C(CH_3)_2-CH_2Br$ $CH_3-C(CH_3)(Br)-CH_2Br$ $CH_3-C(CH_2Br)_2-CH_2Br$

PROBLEM 39♦

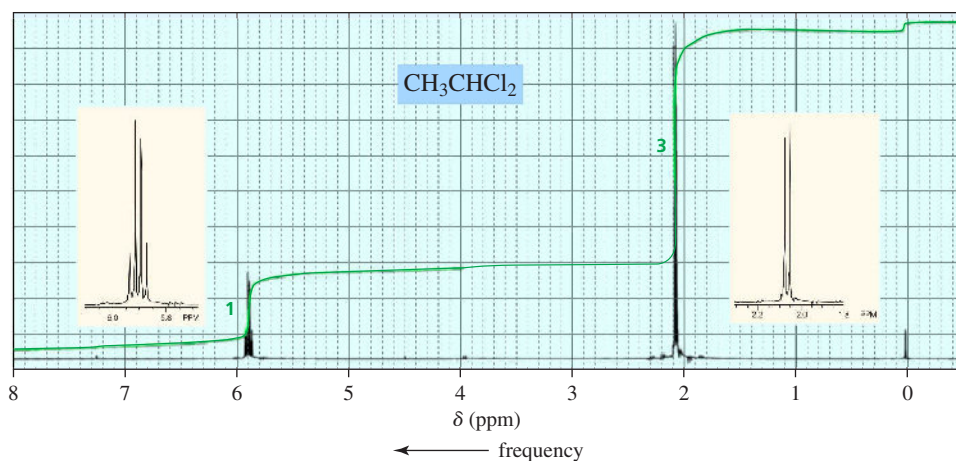
Which of the following compounds is responsible for the ^{1}H NMR spectrum shown here?

$HC\equiv C-C_6H_4-C\equiv CH$ **A**

$CH_3-C_6H_4-CH_3$ **B**

$ClCH_2-C_6H_4-CH_2Cl$ **C**

$Br_2CH-C_6H_4-CHBr_2$ **D**

10.27 THE SPLITTING OF SIGNALS IS DESCRIBED BY THE $N + 1$ RULE

Notice that the shapes of the signals in the ^{1}H NMR spectrum in Figure 10.28 are different from the shapes of the signals in the ^{1}H NMR spectrum in Figure 10.27. Both signals in Figure 10.27 are **singlets,** meaning each is composed of a single peak. In contrast, the signal for the methyl protons in Figure 10.28 (the lower-frequency signal) is split into two peaks (a **doublet**), and the signal for the methine proton is split into four peaks (a **quartet**). (Magnifications of the frequency axis for the doublet and quartet are shown as insets in Figure 10.28; integration numbers are shown in green.)

▲ Figure 10.28
The ^{1}H NMR spectrum of 1,1-dichloroethane. The higher-frequency signal (due to C*H*Cl_2) is an example of a quartet; the lower-frequency signal (due to C*H*$_3$) is a doublet.

Splitting is caused by protons bonded to *adjacent* carbons. The splitting of a signal is described by the **$N + 1$ rule,** where N is the number of equivalent protons bonded to *adjacent* carbons that are not equivalent to the proton producing the signal. Both signals in Figure 10.27 are singlets; the three methyl groups give an unsplit signal because they are attached to a carbon that is not bonded to a hydrogen; the methylene group also gives an unsplit signal because it too is attached to a carbon that is not bonded to a hydrogen ($N = 0$, so $N + 1 = 1$).

In contrast, the carbon adjacent to the methyl group in Figure 10.28 is bonded to one proton ($CHCl_2$), so the signal for the methyl protons is split into a doublet ($N = 1$, so $N + 1 = 2$). The carbon adjacent to the carbon bonded to the methine proton is bonded to three equivalent protons (CH_3), so the signal for the methine proton is split into a quartet ($N = 3$, so $N + 1 = 4$).

The number of peaks in a signal is called the **multiplicity** of the signal. Splitting is always mutual: if the ***a*** protons split the ***b*** protons, then the ***b*** protons must split the ***a*** protons. The ***a*** and ***b*** protons, in this case, are *coupled protons*. **Coupled protons** split each other's signal. Notice that *coupled protons are bonded to adjacent carbons.*

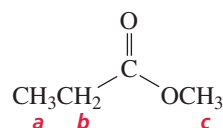
An ^{1}H NMR signal is split into $N + 1$ peaks, where N is the number of equivalent protons bonded to adjacent carbons that are not equivalent to the proton producing the signal.

Keep in mind that it is not the number of protons producing a signal that determines the multiplicity of the signal; rather, it is the number of protons bonded to the immediately adjacent carbons that determines the multiplicity. For example, the signal for the ***a*** protons in the following compound will be split into three peaks (a **triplet**) because the adjacent carbon is bonded to two protons. The signal for the ***b*** protons will appear as a quartet because the adjacent carbon is bonded to three protons, and the signal for the ***c*** protons will be a singlet.

$$\underset{a}{CH_3}\underset{b}{CH_2}-\overset{\overset{\large O}{\|}}{C}-\underset{c}{OCH_3}$$

Coupled protons are bonded to adjacent carbons.

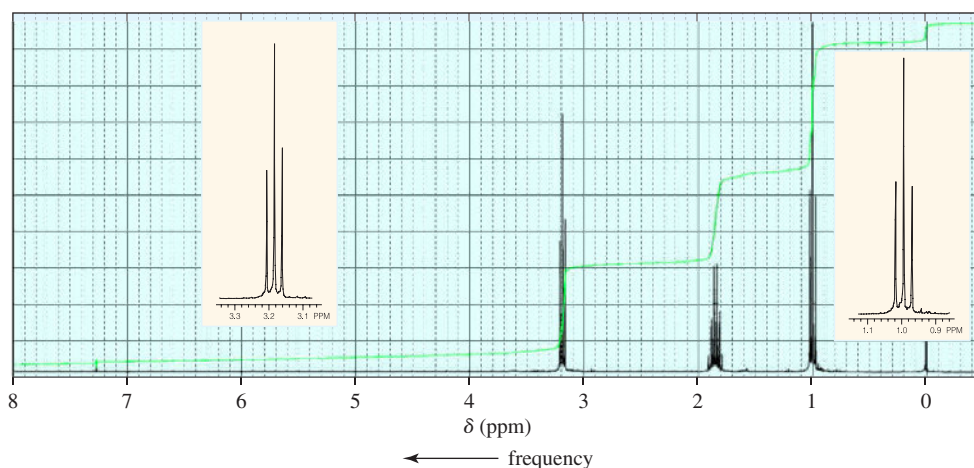
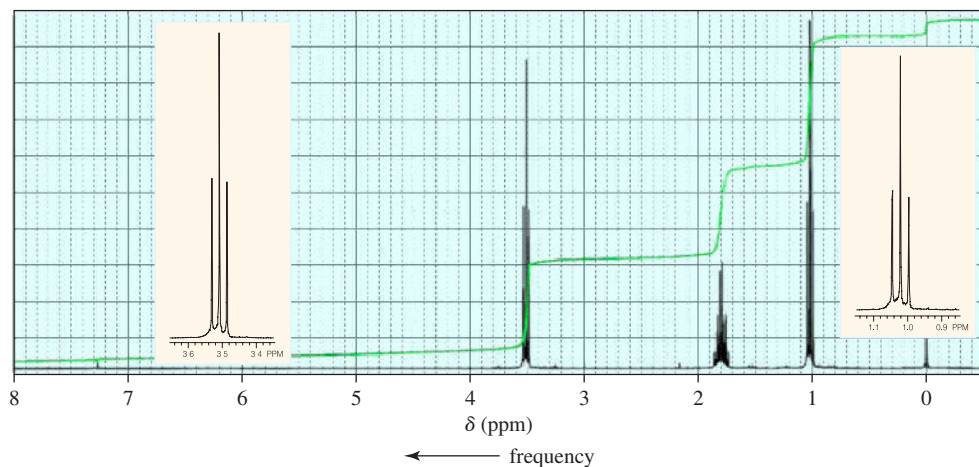
Coupled protons split each other's signal.

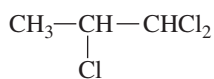
Equivalent protons do not split each other's signal.

A signal for a proton is never split by *equivalent* protons. For example, the ^{1}H NMR spectrum of bromomethane shows one singlet. The three methyl protons are chemically equivalent, and chemically equivalent protons do not split each other's signal. The four protons in 1,2-dichloroethane are also chemically equivalent, so its ^{1}H NMR spectrum also shows one singlet.

CH_3Br	$ClCH_2CH_2Cl$
bromomethane	**1,2-dichloroethane**

each compound shows one singlet in its ^{1}H NMR spectrum because equivalent protons do not split each other's signals

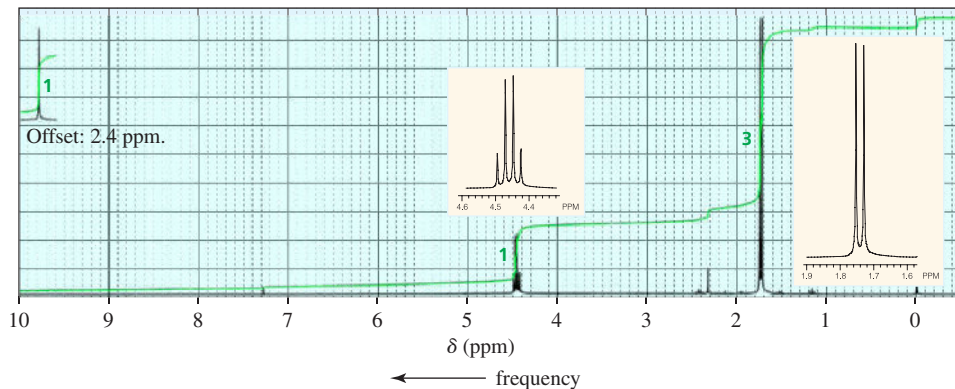
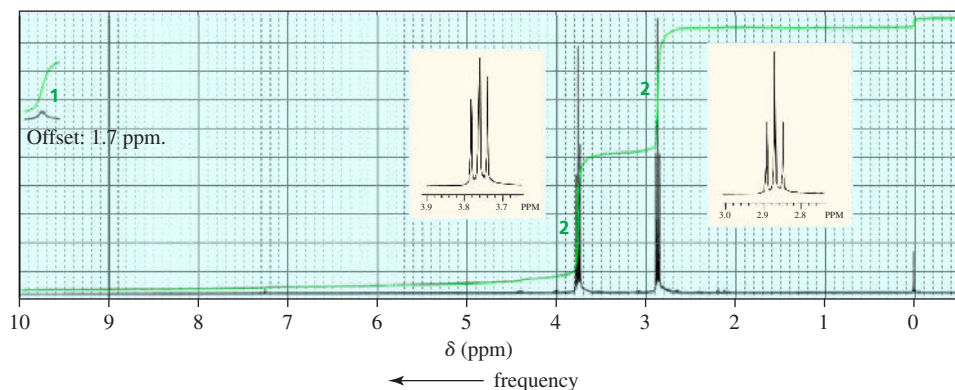
PROBLEM 40

One of the spectra shown here is produced by 1-chloropropane and the other by 1-iodopropane. Which is which?

PROBLEM 41

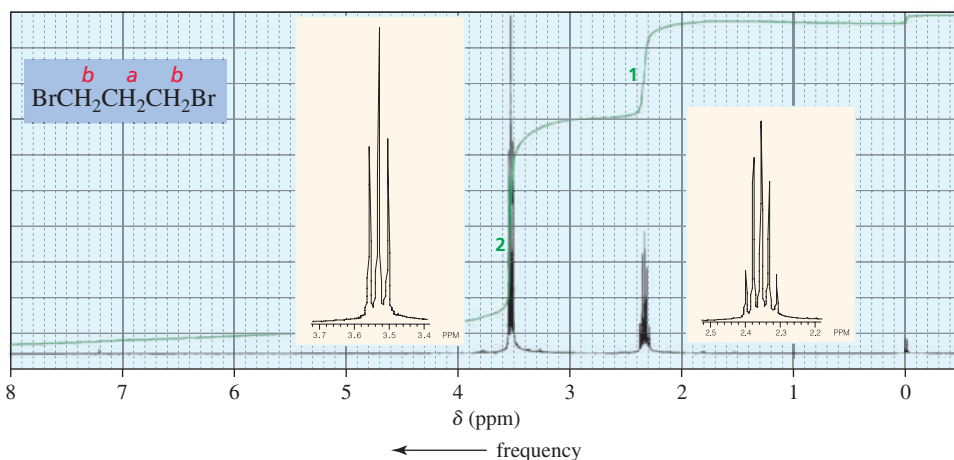
Explain how the following compounds, each with the same molecular formula, could be distinguished by their ^{1}H NMR spectra.

$ClCH_2—CH_2—CHCl_2$ (A) $\quad CH_3—CH(Cl)—CHCl_2$ (B) $\quad CH_3—CH_2—CCl_3$ (C)

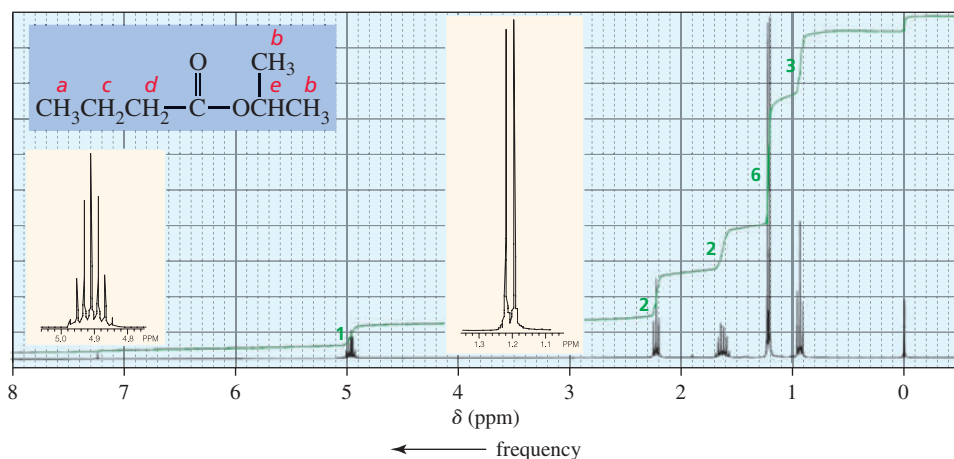
PROBLEM 42♦

The ^{1}H NMR spectra of two carboxylic acids with molecular formula $C_3H_5O_2Cl$ are shown here. Identify the carboxylic acids. (The "offset" notation means that the farthest-left signal has been moved to the right by the indicated amount in order to fit on the spectrum; thus, the signal at 9.8 ppm offset by 2.4 ppm has an actual chemical shift of $9.8 + 2.4 = 12.2$ ppm.)

a.

b.

10.28 MORE EXAMPLES OF ^{1}H NMR SPECTRA

We will now look at a few more spectra to give you additional practice in analyzing ^{1}H NMR spectra.

There are two signals in the ^{1}H NMR spectrum of 1,3-dibromopropane (Figure 10.29). The signal for the ***b*** protons is split into a triplet by the ***a*** protons. The protons on the two carbons adjacent to the one bonded to the ***a*** protons are equivalent. Because the two sets of protons are equivalent, the $N + 1$ rule is applied to both sets at the same time when determining the splitting of the signal for the ***a*** protons. In other words, N is equal to the sum of the equivalent protons on both carbons. Thus, the signal for the ***a*** protons is split into a quintet ($4 + 1 = 5$). Integration confirms that two methylene groups contribute to the higher-frequency signal because it shows that twice as many protons produce that signal than the lower-frequency signal.

▲ Figure 10.29
The ^{1}H NMR spectrum of 1,3-dibromopropane. The quintet corresponds to H_a and the triplet corresponds to H_b.

The ^{1}H NMR spectrum in Figure 10.30 shows five signals. The signal for the ***a*** protons is split into a triplet by the ***c*** protons; and the signal for the ***b*** protons is split into a doublet by the ***e*** proton. The signal for the ***c*** protons is split into a multiplet by the ***a*** and ***d*** protons (the $N + 1$ rule is applied separately to the ***a*** and ***d*** protons). The signal for the ***d*** protons is split into a triplet by the ***c*** protons; and the signal for the ***e*** proton is split into a septet by the ***b*** protons (the $N + 1$ rule is applied to both sets of ***b*** protons at the same time).

▲ Figure 10.30
The ^{1}H NMR spectrum of isopropyl butanoate.

PROBLEM 43

Indicate the number of signals and the multiplicity of each signal in the ^{1}H NMR spectrum of each of the following compounds:

a. $CH_3CH_2CH_2CH_2CH_2CH_3$ **b.** $ICH_2CH_2CH_2Br$ **c.** $ClCH_2CH_2CH_2Cl$ **d.** $ICH_2CH_2CHBr_2$

Ethylbenzene has five sets of chemically equivalent protons (Figure 10.31). We see the expected triplet for the ***a*** protons and the quartet for the ***b*** protons. (This is the characteristic pattern for an ethyl group.) The five protons attached to the benzene ring are not all in the same environment, so we expect to see three signals for them; one for the H_c protons, one for the H_d protons, and one for the H_e proton. However, we do not see three distinct signals because their environments are not sufficiently different to allow them to appear as separate signals.

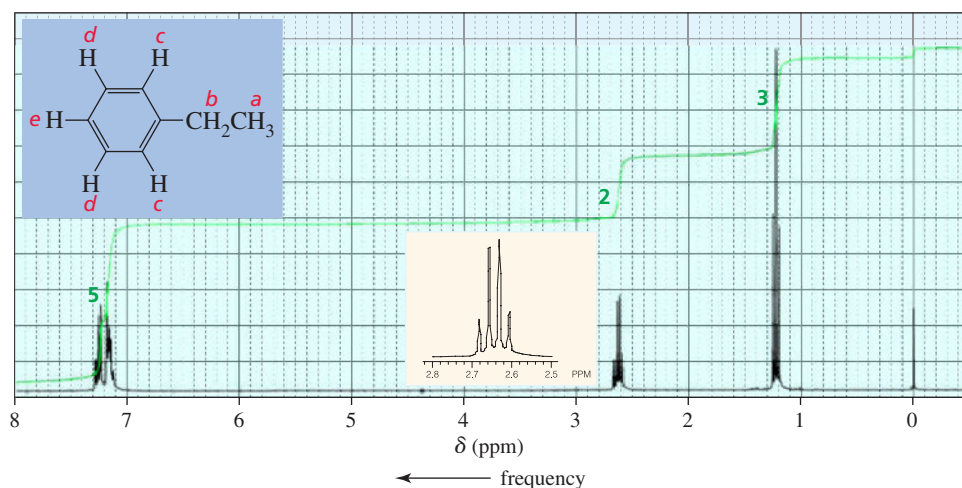



Figure 10.31
The ^{1}H NMR spectrum of ethylbenzene. The signals for the ***c, d,*** and ***e*** protons overlap.

Signals for benzene ring protons occur in the 6.5 to 8.0 ppm region (Table 10.6). Other kinds of protons usually do not resonate in this region, so signals in this region indicate that the compound has a benzene ring. Therefore, the signals at 7.1 to 7.3 ppm in Figure 10.31 are assigned to the benzene ring protons.

Let's now summarize the kind of information that can be obtained from an ^{1}H NMR spectrum:

1. The number of signals indicates the minimum number of different kinds of protons in the compound. (There could be more if there is overlap.)
2. The position of a signal indicates the kind of proton(s) that produce the signal (methyl, methylene, methine, allylic, vinylic, benzene, and so on) and the kinds of neighboring substituents.
3. The integration of the signal tells the relative number of protons that produce the signal.
4. The multiplicity of the signal ($N + 1$) tells the number of protons (N) bonded to adjacent carbons.

PROBLEM 44

How would the ^{1}H NMR spectra for the four compounds with molecular formula $C_3H_6Br_2$ differ?

PROBLEM 45

Predict the splitting patterns for the signals given by each of the compounds in Problem 31.

PROBLEM 46

Describe the ^{1}H NMR spectrum you would expect for each of the following compounds, indicating the relative positions of the signals:

a. $BrCH_2CH_2CH_2CH_2Br$

b. $CH_3OCH_2CH_2CH_2Br$

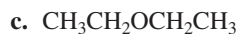
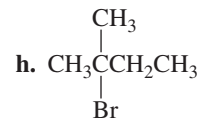
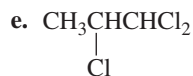
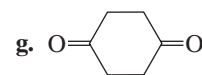
c. $CH_3CH_2OCH_2CH_3$

d. $CH_3CH_2OCH_2Cl$

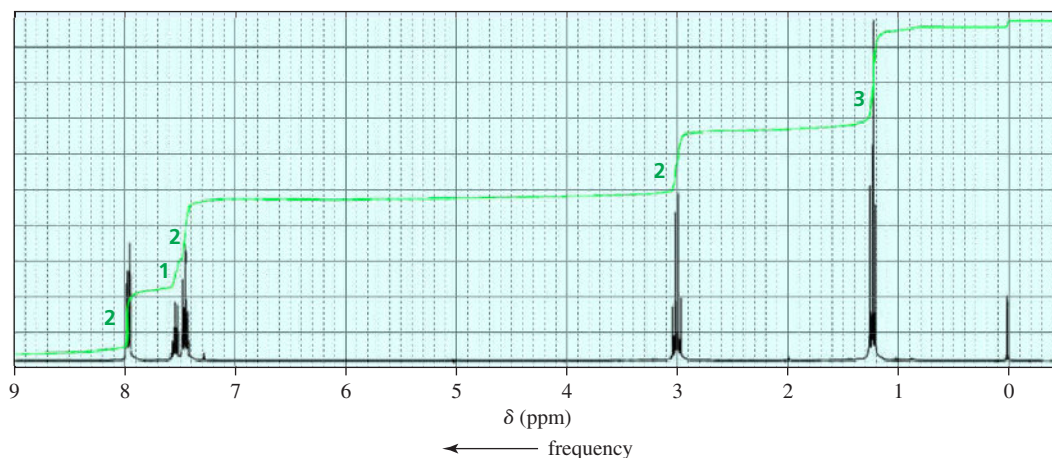
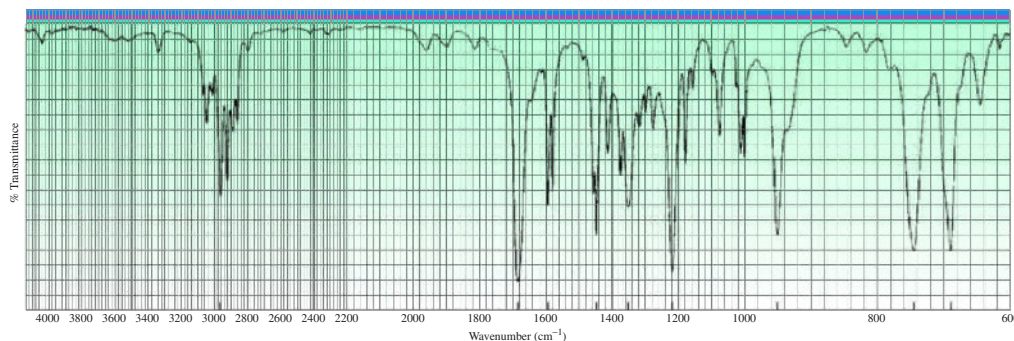
e. $CH_3CH(Cl)CHCl_2$

f. $CH_3OCH_2CH_2CH_2OCH_3$

g. O=⟨cyclohexane⟩=O (1,4-cyclohexanedione)

h. $CH_3C(CH_3)(Br)CH_2CH_3$

PROBLEM-SOLVING STRATEGY

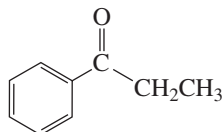
Using IR and ^{1}H NMR Spectra to Deduce a Chemical Structure

Identify the compound with molecular formula $C_9H_{10}O$ that gives the IR and ^{1}H NMR spectra shown here.

One way to approach this kind of problem is to identify whatever structural features you can from the ^{1}H NMR spectrum and then use the information from the molecular formula and the IR spectrum to expand on that knowledge.

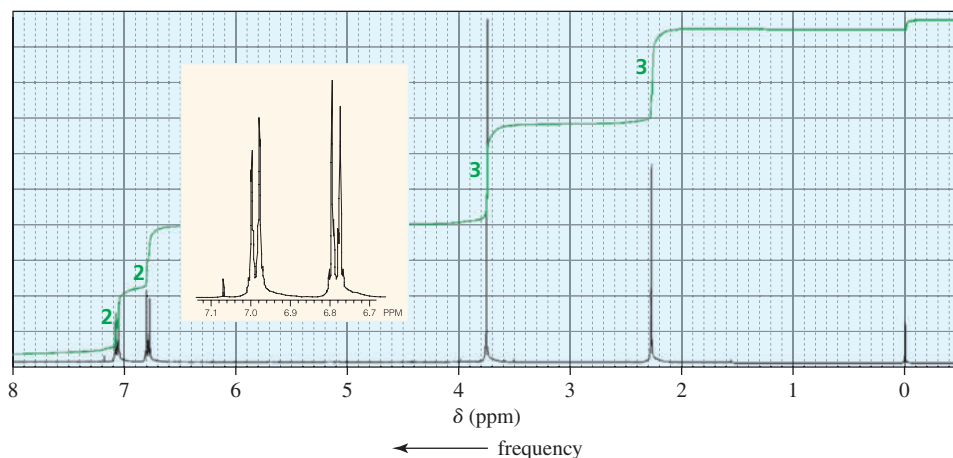
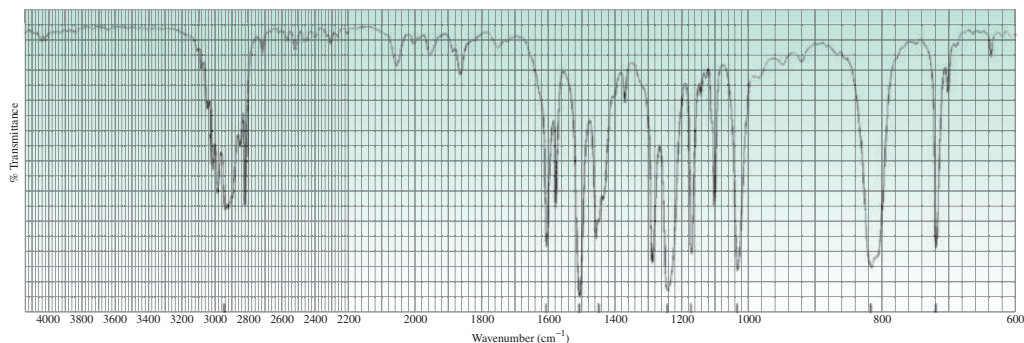
The signals in the 7.4 to 8.0 ppm region of the NMR spectrum indicate a benzene ring; since the signals integrate to 5H, we know it is a monosubstituted benzene ring. The triplet at ~1.2 ppm and the quartet at ~3.0 ppm indicate an ethyl group that is attached to an electron-withdrawing group.

From the molecular formula and the IR spectrum, we learn that the compound is a ketone: it has a carbonyl group at ~1680 cm^{-1}, only one oxygen, and no absorption bands at ~2820 and ~2720 cm^{-1} that would indicate an aldehyde. The carbonyl group absorption band is at

a lower frequency than is typical, which suggests that it has partial single-bond character as a result of electron delocalization, indicating that it is attached to an sp^2 carbon. Now we can conclude that the compound is the ketone shown here. The integration ratio (5 : 2 : 3) confirms this answer.

O
‖
C
CH_2CH_3

Now use the strategy you have just learned to solve Problem 47.

PROBLEM 47♦

Identify the compound with molecular formula $C_8H_{10}O$ that gives the IR and ^1H NMR spectra shown here.

10.29 ^{13}C NMR SPECTROSCOPY

The number of signals in a **^{13}C NMR** spectrum tells how many different kinds of carbons a compound has—just as the number of signals in an ^{1}H NMR spectrum tells how many different kinds of hydrogens a compound has. The principles behind ^{1}H NMR and ^{13}C NMR spectroscopy are essentially the same.

One advantage to ^{13}C NMR spectroscopy is that the chemical shifts of carbon atoms range over about 220 ppm (Table 10.7), compared with over 12 ppm for hydrogens (Table 10.6). This means that signals for carbons in different environments are more easily distinguished. For example, the data in Table 10.7 show that aldehyde (190 to 200 ppm) and ketone (205 to 220 ppm) carbonyl groups can be distinguished from each other and from other carbonyl groups.

The reference compound used in ^{13}C NMR is TMS, the same reference compound used in ^{1}H NMR. You will find it helpful when analyzing a ^{13}C NMR spectrum to divide it into five regions and remember the kind of carbons that show signals in each region.

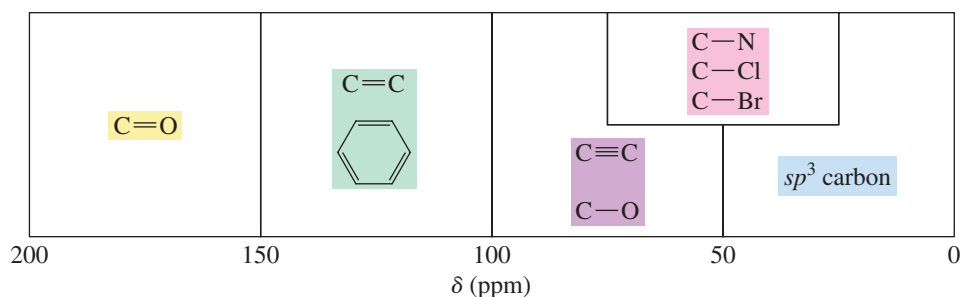



Table 10.7 Approximate Values of Chemical Shifts (ppm) for ^{13}C NMR

Type of carbon	ppm	Type of carbon	ppm	Type of carbon	ppm	Type of carbon	ppm
$(CH_3)_4Si$	0	C≡C	70–90	C—Cl	25–50	RC(=O)OH (HO—C=O)	175–185
R—CH_3	0–35	C≡N	110–120	C—N	40–60	RC(=O)H (H—C=O)	190–200
R—CH_2—R	15–55	C=C	100–150	C—O	50–90	RC(=O)R (R—C=O—R)	205–220
R—CH(R)—R	25–55	C=N	150–170	RC(=O)N<	165–175		
R—C(R)(R)—R	30–40	C (benzene ring)	110–170	RC(=O)OR (RO—C=O)	165–175		
		C—I	−20–10				
		C—Br	10–40				

A disadvantage of ^{13}C NMR spectroscopy is that, unless special techniques are used, the area under a ^{13}C NMR signal is *not* proportional to the number of carbons that produce the signal. Thus, the number of carbons that produce a particular ^{13}C NMR signal cannot routinely be determined by integration.

The ^{13}C NMR spectrum of 2-butanol shows four signals (Figure 10.32), so we know that it has carbons in four different environments. The relative positions of the signals depend on the same factors that determine the relative positions of the proton signals in an ^{1}H NMR spectrum—namely, carbons in electron-rich environments produce low-frequency signals, whereas carbons close to electron-withdrawing groups produce high-frequency signals.

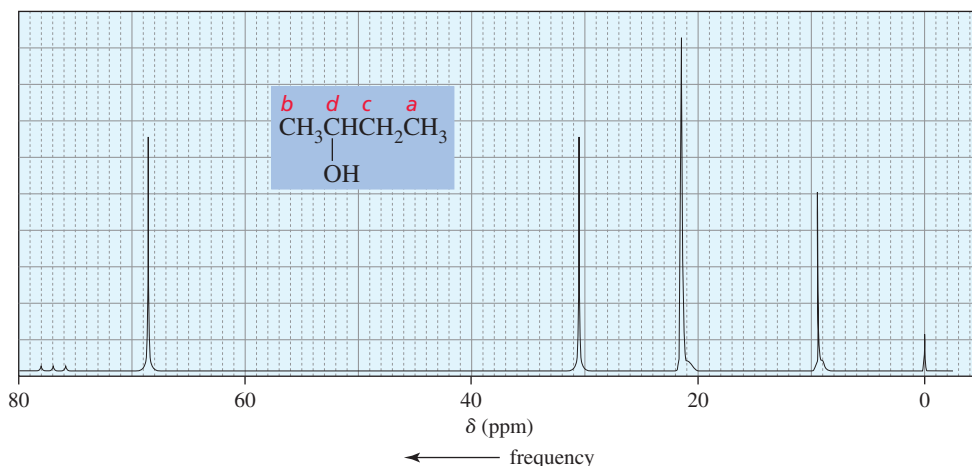



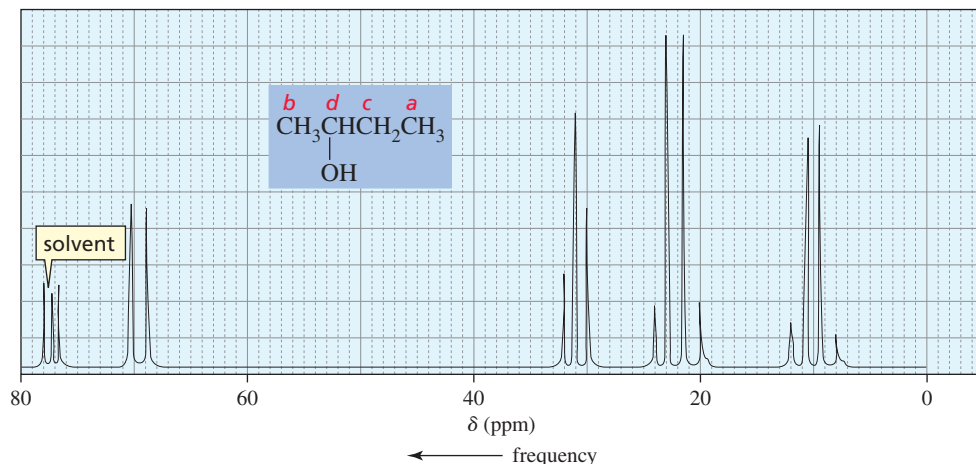
Figure 10.32
The ^{13}C NMR spectrum of 2-butanol.

This means that the signals for the carbons of 2-butanol are in the same relative order as the signals of the protons bonded to those carbons in its ^{1}H NMR spectrum.

Thus, the carbon of the methyl group farthest away from the electron-withdrawing OH group gives the lowest-frequency signal. The other methyl carbon comes next in order of increasing frequency, followed by the methylene carbon; the carbon attached to the OH group gives the highest-frequency signal.

The signals in ^{13}C NMR are not normally split by neighboring carbons because there is little likelihood of an adjacent carbon being a ^{13}C since it constitutes only 1.11% of naturally occurring carbon. Thus, all the signals are singlets in an ordinary ^{13}C NMR spectrum (Figure 10.32).

However, if the spectrometer is run in a *proton-coupled* mode, then each signal will be split by the *hydrogens* bonded to the carbon that produces the signal. The multiplicity of the signal is determined by the $N + 1$ rule.

The **proton-coupled ^{13}C NMR spectrum** of 2-butanol is shown in Figure 10.33. The signals for the methyl carbons are each split into a quartet because each methyl carbon is bonded to three hydrogens ($3 + 1 = 4$). The signal for the methylene carbon is split into a triplet because the carbon is bonded to two hydrogens ($2 + 1 = 3$), and the signal for the carbon bonded to the OH group is split into a doublet because the carbon is bonded to one hydrogen ($1 + 1 = 2$). (The signal at 77 ppm is produced by the solvent, $CDCl_3$.)

If the spectrometer is run in a proton-coupled mode, splitting by the directly attached protons is observed in a ^{13}C NMR spectrum.

▲ **Figure 10.33**
The proton-coupled ^{13}C NMR spectrum of 2-butanol. Each signal is split by the hydrogens bonded to the carbon that produces the signal, according to the $N + 1$ rule.

PROBLEM 48

Answer the following questions for each of the following compounds:

a. How many signals are in its ^{13}C NMR spectrum?
b. Which signal is at the lowest frequency?

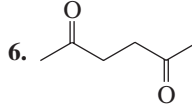
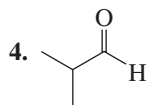
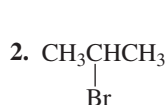
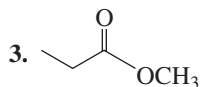
1. $CH_3CH_2CH_2Br$

2. CH_3CHCH_3 (with Br on the central carbon)

3. O, OCH_3

4. O, H

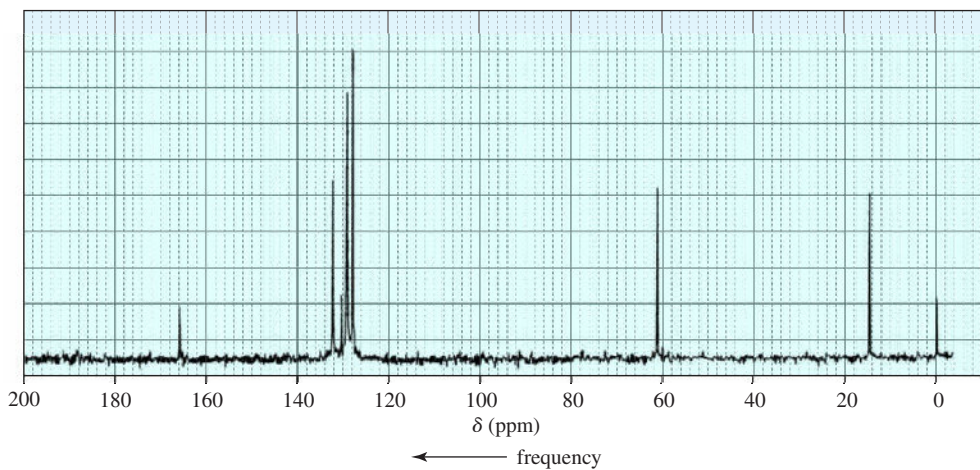
5. O

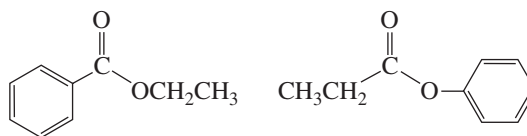
6. O, O

PROBLEM 49

Describe the proton-coupled ^{13}C NMR spectra for compounds 1, 2, and 4 in Problem 48, indicating the relative positions of the signals.

PROBLEM-SOLVING STRATEGY

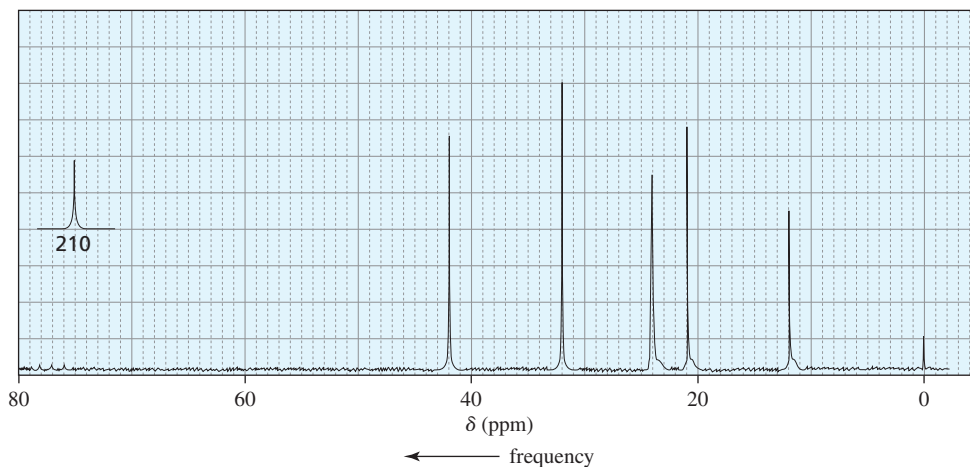
Deducing a Chemical Structure from a ^{13}C NMR Spectrum

Identify the compound with molecular formula $C_9H_{10}O_2$ that gives the following ^{13}C NMR spectrum:

First, pick out the signals that can be identified easily. For example, the signal for the carbonyl carbon at 166 ppm and the two oxygens in the molecular formula indicate that the compound is an ester. The four signals at about 130 ppm suggest that the compound has a benzene ring with a single substituent. (One signal is for the carbon to which the substituent is attached, one signal is for the two adjacent carbons, and so on.) Subtracting those fragments (C_6H_5 and CO_2) from the molecular formula of the compound leaves C_2H_5, the molecular formula of an ethyl substituent. Therefore, we know that the compound is one of the following two compounds.

$C_6H_5C(=O)OCH_2CH_3$ $\qquad$ $CH_3CH_2C(=O)O{-}C_6H_5$

Since the signal for the methylene group is at ~60 ppm, it must be adjacent to an oxygen. Thus, the compound is the one on the left.

Now use the strategy you have just learned to solve Problem 50.

PROBLEM 50♦

Identify the compound with a molecular formula of $C_{11}H_{22}O$ that gives the ^{13}C NMR spectrum shown here.

NMR Used in Medicine is Called Magnetic Resonance Imaging

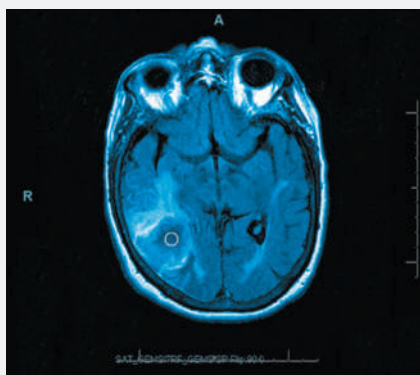
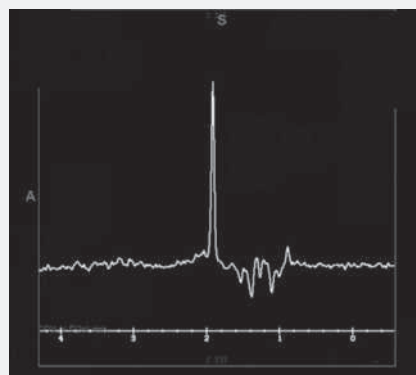
NMR has become an important tool in medical diagnosis because it allows physicians to examine internal organs and structures without resorting to surgery or to the harmful ionizing radiation of X-rays. When NMR was first introduced into clinical practice in 1981, the selection of an appropriate name was a matter of some debate. Because many members of the general public associate the word *nuclear* with harmful radiation or radioactivity, the "N" was dropped from the medical application of NMR, which is known as **magnetic resonance imaging (MRI).** The spectrometer is called an **MRI scanner.**

An MRI scanner consists of a magnet large enough to surround a person, along with an apparatus for exciting the nuclei, modifying the magnetic field, and receiving signals. (By comparison, the NMR spectrometer used by chemists is only large enough to accommodate a 5-mm glass tube.) Different tissues yield different signals, which are separated into components. Each component can be attributed to a specific location within the part of the body being scanned, so that a set of images through the scanned volume is generated. MRI can produce an image showing any cross section of the body, regardless of the person's position within the machine, and takes an average of about only two minutes to obtain.

Most of the signals in an MRI scan originate from the hydrogens of water molecules because tissues contain far more of these hydrogens than they do hydrogens of organic compounds. The difference in the way water is bound in different tissues is what produces much of the variation in signal between different organs, as well as the variation between healthy and diseased tissue. MRI scans, therefore, can provide much more information than images obtained by other means.

For example, MRI can provide detailed images of blood vessels. Flowing fluids, such as blood, respond differently to excitation in an MRI scanner than do stationary tissues, and proper processing will result in the display of only the moving fluids. The quality of these images has become high enough that it can often eliminate the need for more invasive diagnostic techniques.

The versatility of MRI has been enhanced by using gadolinium as a contrast agent. Gadolinium modifies the magnetic field in its immediate vicinity, altering the signal from nearby hydrogens. The distribution of gadolinium, which is infused into a patient's veins, may be affected by certain disease processes such as cancer and inflammation. Any abnormal patterns of distribution are revealed in the MRI images.

A brain tumor and a brain abscess may have very similar appearances in an MRI. Suppressing the signal from water makes it possible to detect signals from specific compounds such as choline and acetate. A tumor will produce an elevated choline signal, whereas an abscess is more likely to produce an elevated acetate signal.

The white circle indicates a brain lesion that could be caused by either a tumor (elevated choline) or an abscess (elevated acetate).

The major peak in the spectrum corresponds to acetate, supporting the diagnosis of an abscess.

SOME IMPORTANT THINGS TO REMEMBER

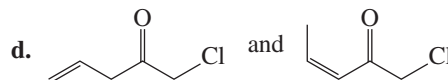
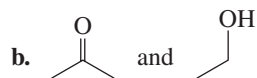
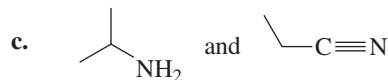
- **Mass spectrometry** allows us to determine the *molecular mass* and the *molecular formula* of a compound and some of its structural features.
- The **molecular ion** (a **radical cation**), which is formed by removing an electron from a molecule, can break apart. The bonds most likely to break are the weakest ones and those that result in the formation of the most stable products.
- A **mass spectrum** is a graph of the relative abundance of each positively charged fragment plotted against its *m*/*z* value. The *m*/*z* value of the molecular ion (M) gives the molecular mass of the compound.
- Peaks with smaller *m*/*z* values—**fragment ion peaks**—represent positively charged fragments of the molecular ion. The **base peak** is the peak with the greatest abundance. It the most stable fragment.
- The **rule of 13** allows possible molecular formulas to be determined from the *m/z* value of the molecular ion.
- High-resolution mass spectrometers determine the exact molecular mass, which allows a compound's molecular formula to be determined.
- The M + 1 peak occurs because of the naturally occurring ^{13}C isotope.
- If the M + 2 peak is one-third the height of the M peak, the compound contains a chlorine atom; if the M and M + 2 peaks are about the same height, the compound contains a bromine atom.
- Electron bombardment is most likely to dislodge a lone-pair electron.
- **Spectroscopy** is the study of the interaction of matter and **electromagnetic radiation.**
- High-energy radiation is associated with *high frequencies, large wavenumbers*, and *short wavelengths*.
- **Infrared (IR) spectroscopy** identifies the kinds of functional groups in a compound. To absorb IR radiation, the dipole moment of the bond must change when the vibration occurs.
- It takes more energy to stretch a bond than to bend it.
- Stronger bonds show **absorption bands** at larger wavenumbers.
- The position of an absorption band depends on bond order, hybridization, inductive electron donation and withdrawal, electron delocalization, and hydrogen bonding.
- The intensity of an absorption band depends on the size of the change in dipole moment (more polar bonds show more intense absorptions) and the number of bonds giving rise to the absorption.
- The shape of an absorption band depends on hydrogen bonding. Hydrogen bonds vary in strength, so hydrogen-bonded groups show broader absorption bands.
- **Ultraviolet** and **visible (UV/Vis) spectroscopy** provide information about compounds with conjugated double bonds—the more conjugated double bonds in a compound, the longer the λ_{max} at which absorption occurs.
- UV light has greater energy than visible light—the shorter the wavelength, the greater the energy.
- **NMR spectroscopy** identifies the carbon–hydrogen framework of an organic compound.
- Each set of chemically equivalent protons produces a signal, so the number of signals in an ^{1}H NMR spectrum indicates the number of different kinds of protons in a compound (unless there are overlapping signals).
- The **chemical shift** (δ) is a measure of how far the signal is from the reference TMS signal. Low-frequency signals have small δ (ppm) values; high-frequency signals have large δ values.
- The larger the magnetic field sensed by the proton, the higher the frequency of its signal.
- The electron density of the environment in which the proton is located **shields** the proton from the applied magnetic field. Therefore, a proton in an electron-dense environment shows a signal at a lower frequency than a proton near electron-withdrawing groups.
- In a similar environment, the chemical shift of a methine proton is at a higher frequency than the chemical shift of methylene protons, which is at a higher frequency than the chemical shift of methyl protons.
- **Integration** tells us the relative number of protons that produce each signal.
- The **multiplicity** of a signal indicates the number of protons bonded to adjacent carbons. Multiplicity is described by the ***N*+1 rule,** where *N* is the number of equivalent protons bonded to an adjacent carbon.
- Coupled protons split each other's signal.
- The number of signals in a ^{13}C NMR spectrum corresponds to the number of different kinds of carbons in the compound. Carbons in electron-rich environments produce low-frequency signals, whereas carbons close to electron-withdrawing groups produce high-frequency signals.
- ^{13}C NMR signals are not split by directly attached protons unless the spectrometer is run in a proton-coupled mode.

PROBLEMS

51. In the mass spectrum of the following compounds, which would be more intense: the peak at $m/z = 57$ or the peak at $m/z = 71$?
a. 3-methylpentane **b.** 2-methylpentane

52. For each of the following pairs of compounds, identify one IR absorption band that could be used to distinguish between them:

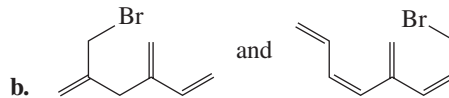
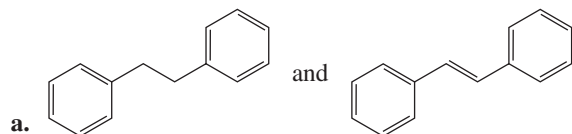
a. OH and O **c.** NH_2 and C≡N

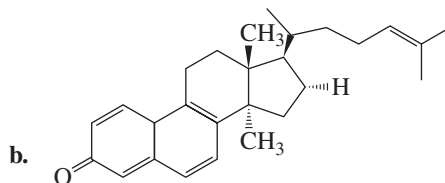
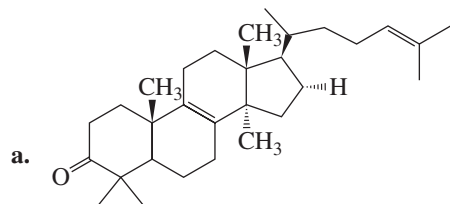
b. O and OH **d.** O Cl and O Cl

53. Draw the structure of a saturated hydrocarbon that has a molecular ion with an m/z value of 100.

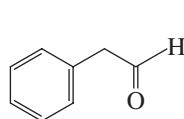
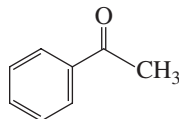
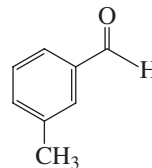
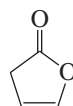
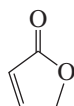
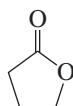
54. A compound gives a mass spectrum with essentially only three peaks at $m/z = 15$ (70%), 57 (55%), and 72 (100%). Identify the compound.

55. What hydrocarbons that contain a five-membered ring will have a molecular ion peak at $m/z = 98$?

56. How could you use UV spectroscopy to distinguish between the compounds in each of the following pairs?

a. and **b.** Br and Br

57. For which of the following compounds would you expect the infrared carbonyl absorption (C=O stretch) to be at a higher frequency? Explain.

a. CH_3 CH_3 H CH_3 O **b.** CH_3 H CH_3 O

58. Predict the relative intensities of the molecular ion peak, the M + 2 peak, and the M + 4 peak for a compound that contains two bromine atoms.

59. A compound is known to be one of those shown here. What absorption bands in its IR spectrum would allow you to identify this compound?

60. List the following compounds in order from highest wavenumber to lowest wavenumber for their C—O absorption bands:

61. How can ^{1}H NMR be used to prove that the addition of HBr to propene follows the rule that says that the electrophile adds to the sp^2 carbon bonded to the most hydrogens?

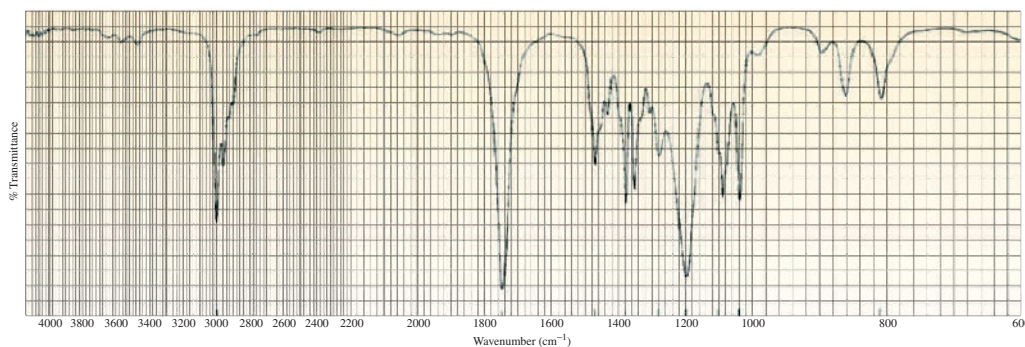
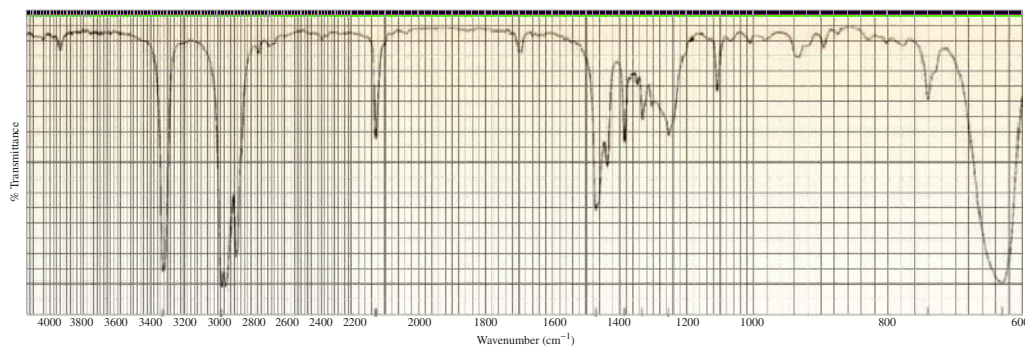
62. There are four dibromopropane with molecular formula $C_3H_6Br_2$. How can they be distinguished by ^{1}H NMR?

63. Would it be better to use ^{1}H NMR or ^{13}C NMR spectroscopy to distinguish among 1-butene, *cis*-2-butene, and 2-methylpropene? Explain your answer.

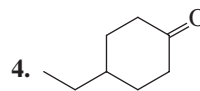
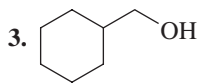
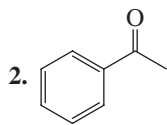
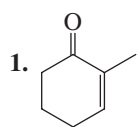
64. Compound **A,** with molecular formula C_4H_9Cl, shows two signals in its ^{13}C NMR spectrum. Compound **B,** an isomer of compound **A,** shows four signals, and in the proton-coupled mode, the signal farthest downfield is a doublet. Identify compounds **A** and **B.**

65. Each of the IR spectra presented here is accompanied by a set of four compounds. In each case, indicate which of the four compounds is responsible for the spectrum.

a. $CH_3CH_2CH_2C{\equiv}CCH_3$ $\quad$ $CH_3CH_2CH_2CH_2OH$ $\quad$ $CH_3CH_2CH_2CH_2C{\equiv}CH$ $\quad$ $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OH$

b. O OH $\quad$ O OCH_2CH_3 $\quad$ O H $\quad$ O

66. How many signals are produced by each of the following compounds in its

a. ^{1}H NMR spectrum? $\quad$ **b.** ^{13}C NMR spectrum?

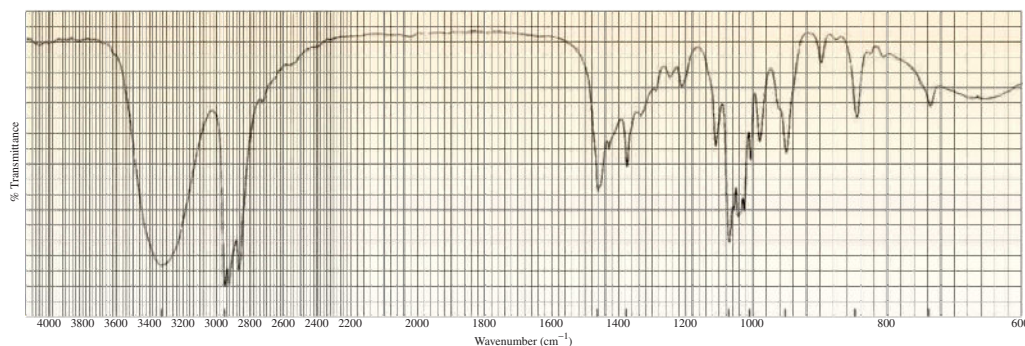
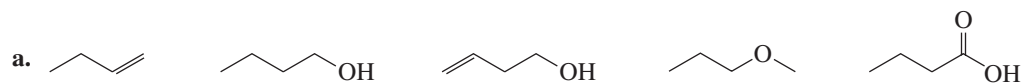
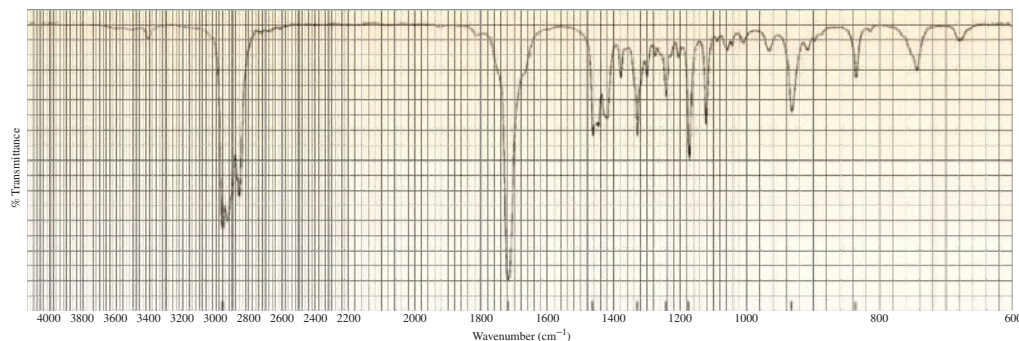
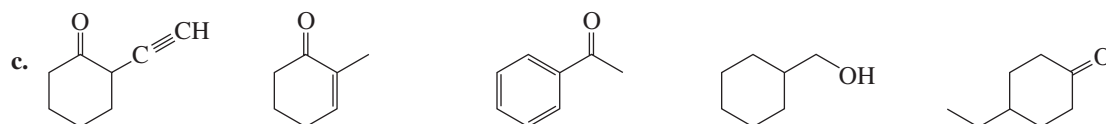
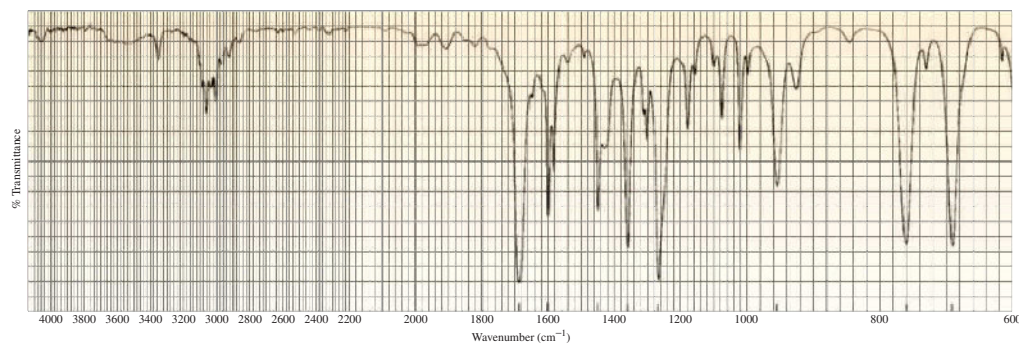
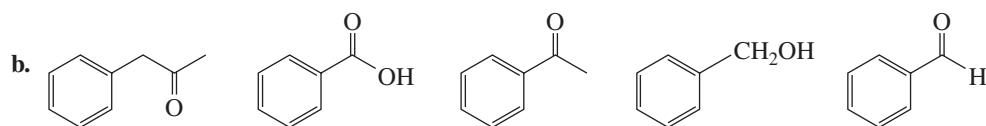
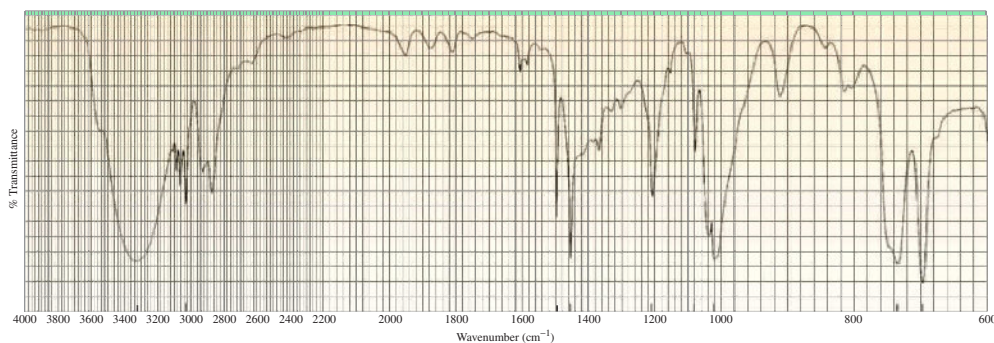
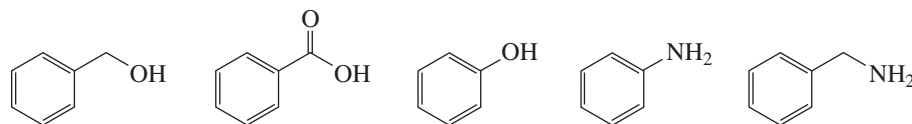
1. O $\quad$ **2.** O $\quad$ **3.** OH $\quad$ **4.** O

67. Five compounds are shown for each of the following IR spectra. Indicate which of the five compounds is responsible for each spectrum.

a.

OH

O OH

b.

c.

68. Which one of the following five compounds produced the IR spectrum shown here?

69. Identify each of the following compounds from the ^{1}H NMR data and molecular formula. The number of hydrogens responsible for each signal is shown in parentheses.

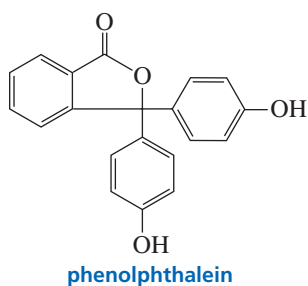
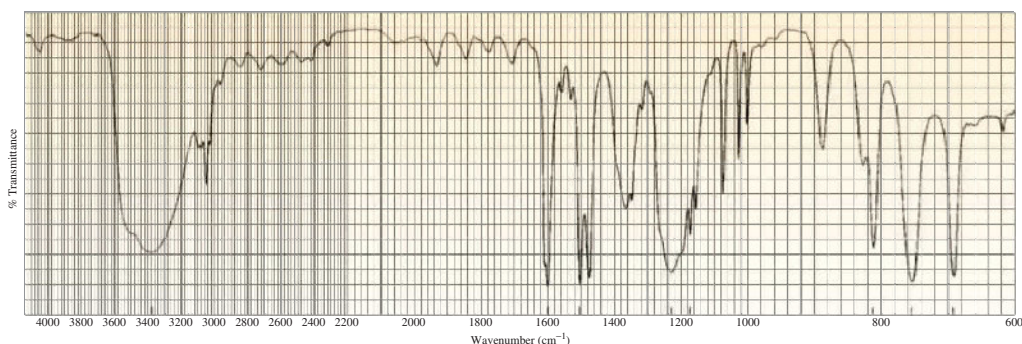
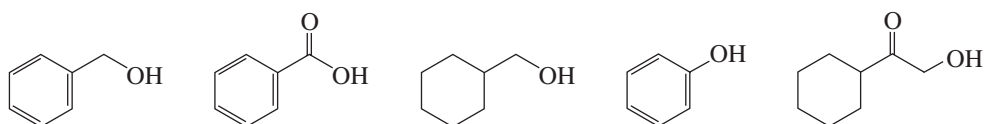
a. $C_4H_8Br_2$ 1.97 ppm (6) singlet
3.89 ppm (2) singlet

b. C_8H_9Br 2.01 ppm (3) doublet
5.14 ppm (1) quartet
7.35 ppm (5) broad multiplet

c. $C_5H_{10}O_2$ 1.15 ppm (3) triplet
1.25 ppm (3) triplet
2.33 ppm (2) quartet
4.13 ppm (2) quartet

70. Phenolphthalein is an acid–base indicator. In solutions of pH < 8.5, it is colorless; in solutions of pH > 8.5, it is deep red-purple. Account for the change in color.

O O OH OH

phenolphthalein

71. Which one of the following five compounds produced the IR spectrum shown here?

72. How could IR spectroscopy distinguish between 1-hexyne, 2-hexyne, and 3-hexyne?

73. Draw the structure of a carboxylic acid that has a molecular ion with an *m/z* value of 116.

74. Label each set of chemically equivalent protons, using ***a*** for the set that will be at the lowest frequency (farthest upfield) in the ^{1}H NMR spectrum, ***b*** for the next lowest, and so on. Indicate the multiplicity of each signal.

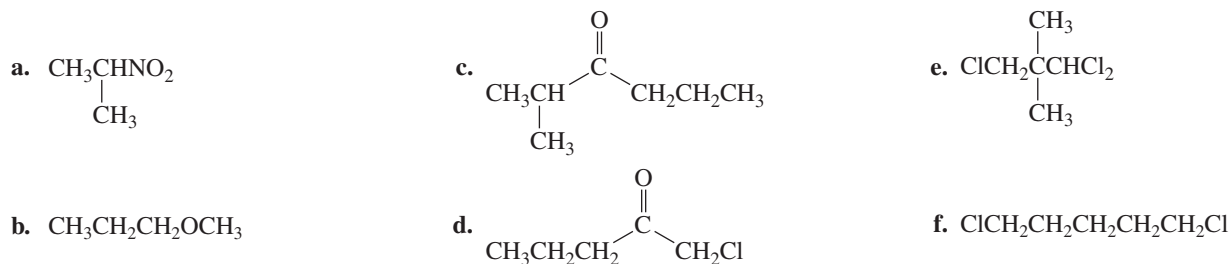
a. CH_3CHNO_2 (with CH_3 on the CH)

b. $CH_3CH_2CH_2OCH_3$

c. $CH_3CH(CH_3)C(=O)CH_2CH_2CH_3$

d. $CH_3CH_2CH_2C(=O)CH_2Cl$

e. $ClCH_2C(CH_3)_2CHCl_2$

f. $ClCH_2CH_2CH_2CH_2CH_2Cl$

75. How could ^{1}H NMR distinguish between the compounds in each of the following pairs?

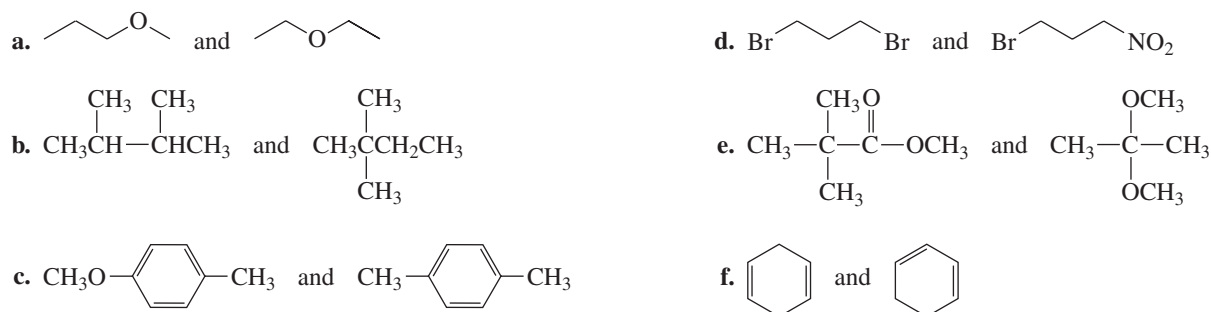
a. O and O

b. $CH_3CH(CH_3)—CH(CH_3)CH_3$ and $CH_3C(CH_3)_2CH_2CH_3$

c. CH_3O—C₆H₄—CH_3 and CH_3—C₆H₄—CH_3

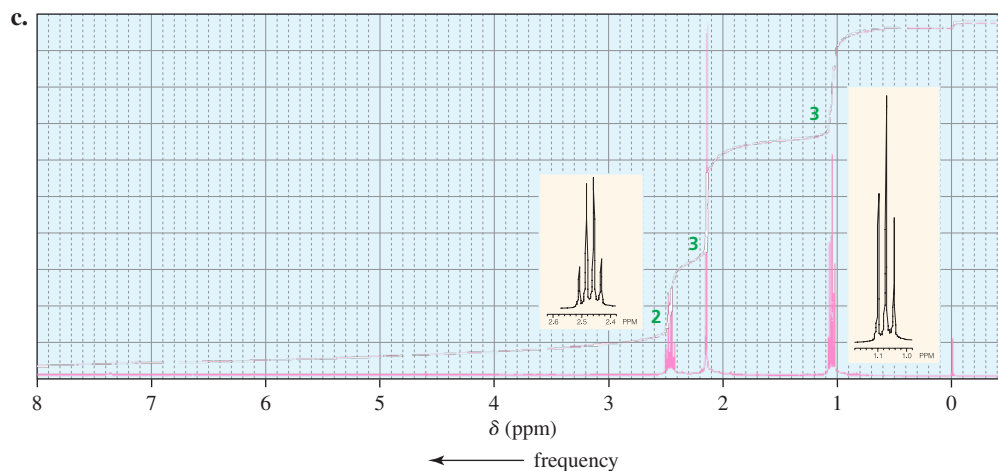
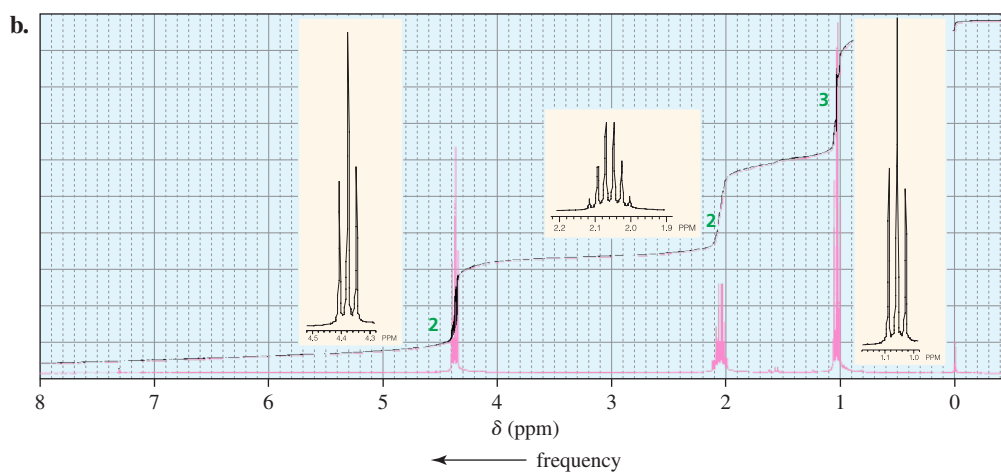
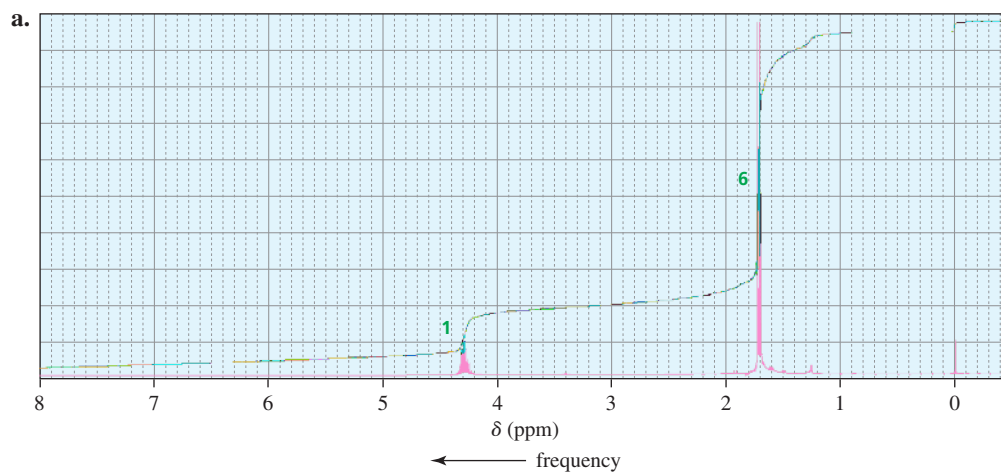
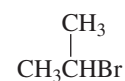
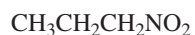
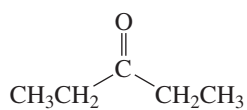
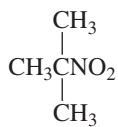
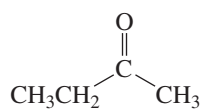
d. Br Br and Br NO_2

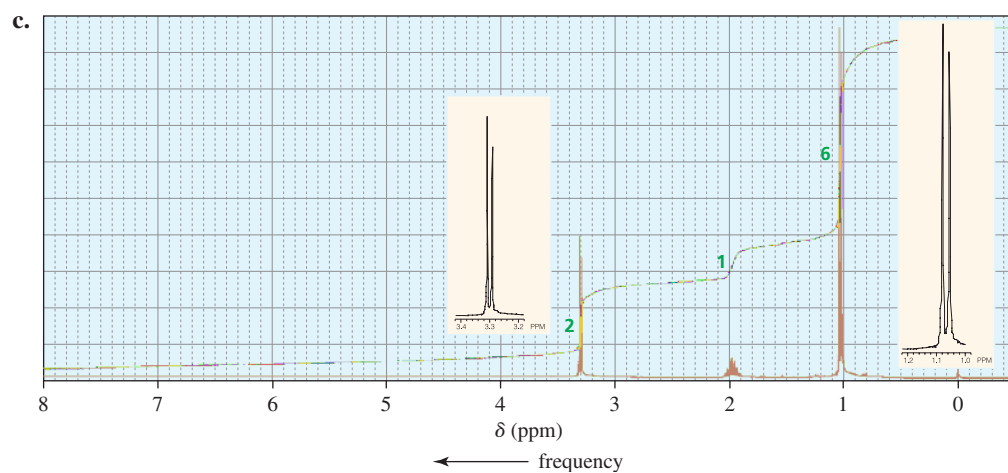
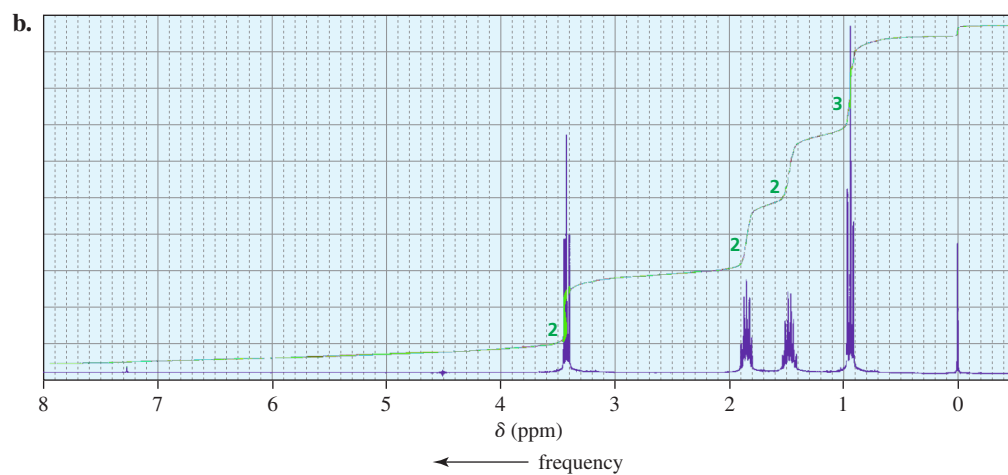
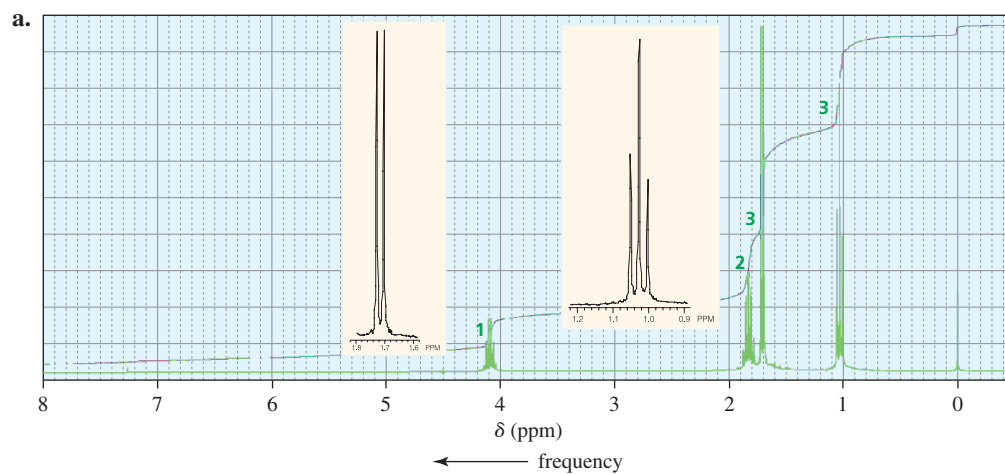
e. $CH_3—C(CH_3)_2—C(=O)—OCH_3$ and $CH_3—C(OCH_3)_2—CH_3$

f. and

76. Match each of the ^{1}H NMR spectra with one of the following compounds:

a.

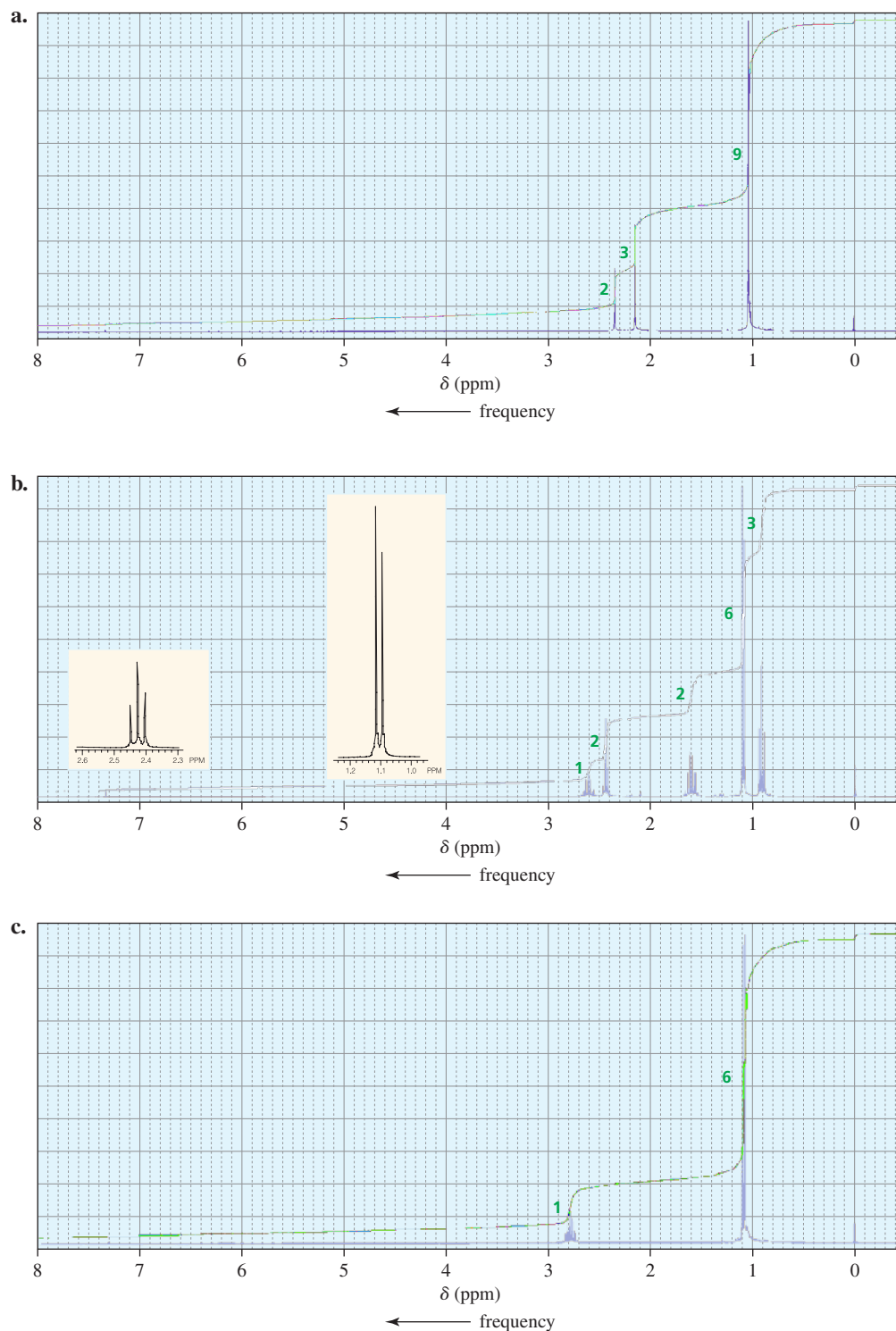
b.

c.

77. Determine the ratios of the chemically nonequivalent protons in a compound if the steps of the integration curves measure 40.5, 27, 13, and 118 mm, from left to right across the spectrum. Draw the structure of a compound whose ^{1}H NMR spectrum would show these integrals in the observed order.

78. The ^{1}H NMR spectra of three isomers with molecular formula C_4H_9Br are shown here. Which isomer produces which spectrum?

79. The ^{1}H NMR spectra of three isomers with molecular formula $C_7H_{14}O$ are shown here. Which isomer produces which spectrum?

a.

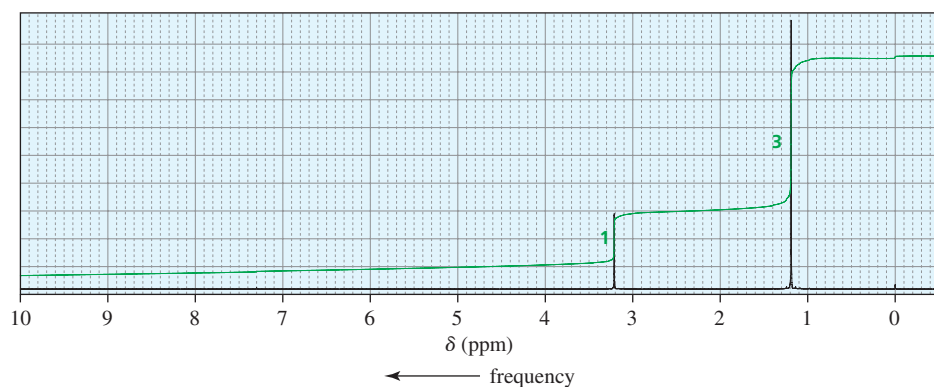
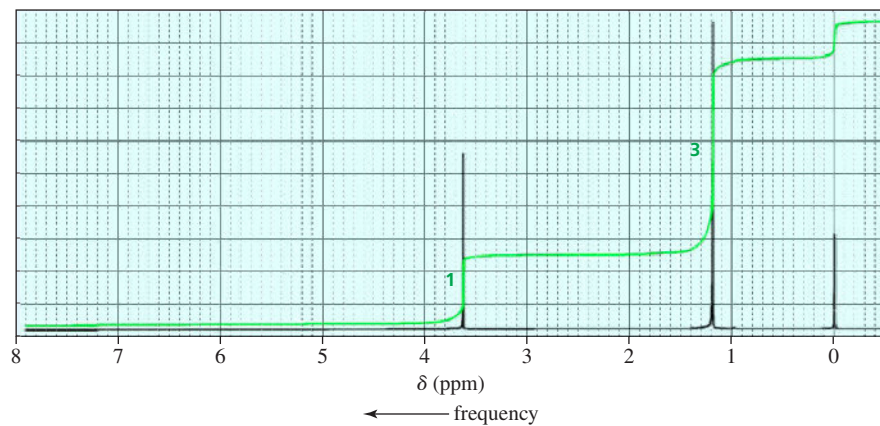
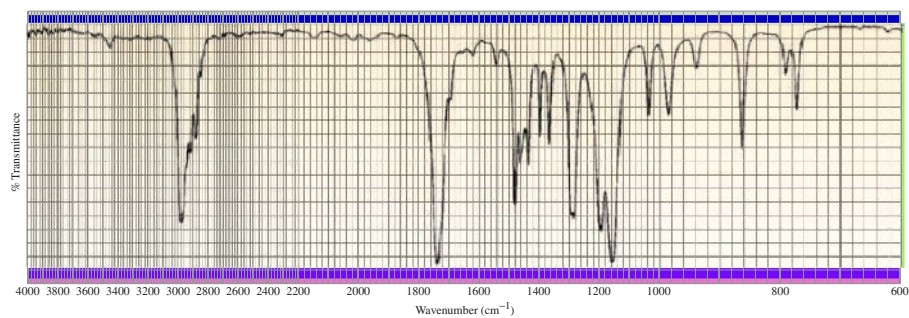
b.

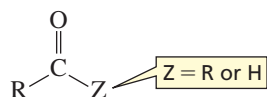
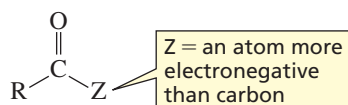
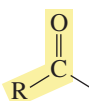
c.

80. Identify the following compounds. (Relative integrals are given from left to right across the spectrum.)

a. The ^{1}H NMR spectrum of a compound with molecular formula $C_4H_{10}O_2$ has two singlets with an area ratio of 2 : 3.

b. The ^{1}H NMR spectrum of a compound with molecular formula $C_6H_{10}O_2$ has two singlets with an area ratio of 2 : 3.

c. The ^{1}H NMR spectrum of a compound with molecular formula $C_8H_6O_2$ has two singlets with an area ratio of 1 : 2.

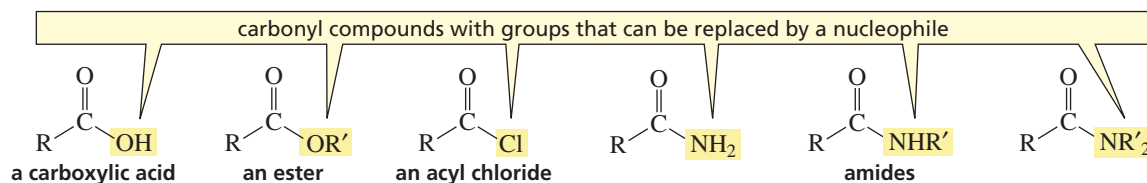
81. An alkyl halide reacts with an alkoxide ion to form a compound whose ^{1}H NMR spectrum is shown here. Identify the alkyl halide and the alkoxide ion. (*Hint:* See Section 8.13.)

82. Determine the structure of a compound with molecular formula $C_6H_{12}O_2$ that gives the following IR and ^{1}H NMR spectra.

11 Reactions of Carboxylic Acids and Carboxylic Acid Derivatives

Group IV

a carbonyl group

an acyl group

Some of the things you will learn in this chapter are how aspirin decreases inflammation and fever, why Dalmatians are the only dogs that excrete uric acid, how bacteria become resistant to penicillin, and why young people sleep better than adults.

We have seen that the families of organic compounds can be placed in one of four groups, and that all the families in a group react in similar ways (Section 5.2). This chapter begins our discussion of the familes of compounds in Group IV—compounds that contain a carbonyl group.

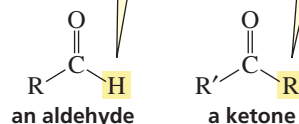
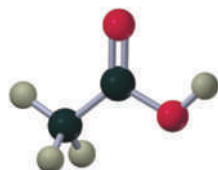
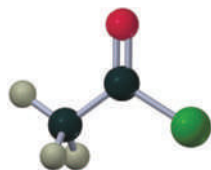
The **carbonyl group** (a carbon doubly bonded to an oxygen) is probably the most important functional group. Compounds containing carbonyl groups—called **carbonyl** ("car-bo-neel") **compounds**—are abundant in nature, and many play important roles in biological processes. Vitamins, amino acids, proteins, hormones, drugs, and flavorings are just a few of the carbonyl compounds that affect us daily. An **acyl group** consists of a carbonyl group attached to an alkyl group (R).

The group (or atom) attached to the acyl group strongly affects the reactivity of the carbonyl compound. In fact, carbonyl compounds can be divided into two classes determined by that group. The first class are those in which the acyl group is attached to a group (or atom) that *can be replaced by another group*. Carboxylic acids, esters, acyl chlorides, and amides belong to this class. All of these compounds contain a group (OH, OR, Cl, NH_2, NHR, NR_2) that can be replaced by a nucleophile.

Esters, acyl chlorides, and amides are called **carboxylic acid derivatives**, because they differ from a carboxylic acid only in the nature of the group or atom that has replaced the OH group of the carboxylic acid.

The second class of carbonyl compounds are those in which the acyl group is attached to a group that *cannot be replaced by another group*. Aldehydes and ketones belong to this class. The H bonded to the acyl group of an aldehyde and the R group bonded to the acyl group of a ketone cannot be replaced by a nucleophile.

carbonyl compounds with groups that cannot be replaced by a nucleophile

$RCOH$ (R–C(=O)–**H**) — **an aldehyde**

$R'COR$ (R′–C(=O)–**R**) — **a ketone**

We have seen that, when comparing bases of the same type, weak bases are good leaving groups and strong bases are poor leaving groups (Section 8.2). The pK_a values of the conjugate acids of the leaving groups of various carbonyl compounds are listed in Table 11.1.

a carboxylic acid
an acyl chloride
an ester
an amide

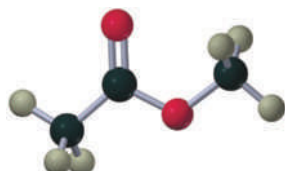
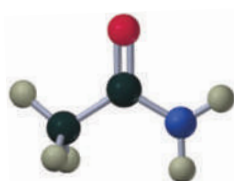



Table 11.1 The pK_a Values of the Conjugate Acids of the Leaving Groups of Carbonyl Compounds

Carbonyl compound	Leaving group	Conjugate acid of the leaving group	pK_a
Carboxylic Acids and Carboxylic Acid Derivatives			
$RCOCl$ (R–C(=O)–Cl)	Cl^-	HCl	–7
$RCOOR'$ (R–C(=O)–OR′)	$^-OR'$	$R'OH$	~15–16
$RCOOH$ (R–C(=O)–OH)	^-OH	H_2O	15.7
$RCONH_2$ (R–C(=O)–NH_2)	$^-NH_2$	NH_3	36*
Aldehydes and Ketones			
$RCOH$ (R–C(=O)–H)	H^-	H_2	35
$RCOR$ (R–C(=O)–R)	R^-	RH	> 60

Notice that the acyl groups of carboxylic acids and carboxylic acid derivatives are attached to weaker bases than are the acyl groups of aldehydes and ketones. (Remember that the lower the pK_a, the stronger the acid and the weaker its conjugate base.) The hydrogen of an aldehyde and the alkyl group of a ketone are too basic to be replaced by another group.

This chapter discusses the reactions of carboxylic acids and carboxylic acid derivatives. We will see that these compounds undergo substitution reactions, because they have an acyl group attached to a group that can be replaced by a nucleophile. The reactions

*An amide can undergo substitution reactions only when its leaving group is converted to NH_3, giving its conjugate acid ($^+NH_4$) a pK_a value of 9.4.

of aldehydes and ketones are discussed in Chapter 12, where we will see that these compounds *do not* undergo substitution reactions, because their acyl group is attached to a group that *cannot* be replaced by a nucleophile.

11.1 THE NOMENCLATURE OF CARBOXYLIC ACIDS AND CARBOXYLIC ACID DERIVATIVES

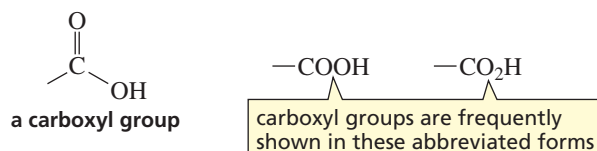
First we will look at how carboxylic acids are named, because their names form the basis of the names of the other carbonyl compounds.

Naming Carboxylic Acids

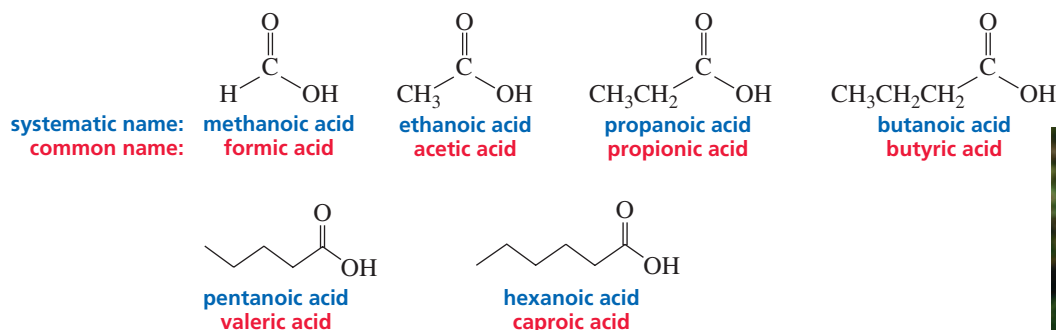
The functional group of a carboxylic acid is called a **carboxyl group.**

$$-C(=O)OH \qquad -COOH \qquad -CO_2H$$

a carboxyl group

carboxyl groups are frequently shown in these abbreviated forms

In systematic (IUPAC) nomenclature, a **carboxylic acid** is named by replacing the terminal "e" of the alkane name with "oic acid." For example, the one-carbon alkane is methan*e*, so the one-carbon carboxylic acid is methan*oic acid*.

	$HC(=O)OH$	$CH_3C(=O)OH$	$CH_3CH_2C(=O)OH$	$CH_3CH_2CH_2C(=O)OH$
systematic name:	methanoic acid	ethanoic acid	propanoic acid	butanoic acid
common name:	formic acid	acetic acid	propionic acid	butyric acid

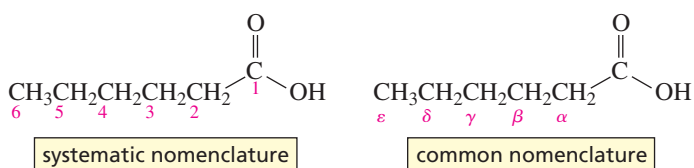
	(pentanoic acid structure)	(hexanoic acid structure)
systematic name:	pentanoic acid	hexanoic acid
common name:	valeric acid	caproic acid

valerian flowers

goats

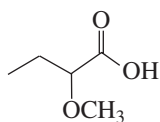
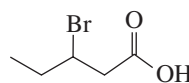
Carboxylic acids containing six or fewer carbons are frequently called by their common names. These names were chosen by early chemists to describe some feature of the compound, usually its origin. For example, formic acid is found in ants, bees, and other stinging insects; its name comes from *formica*, which is Latin for "ant." Acetic acid—contained in vinegar—got its name from *acetum*, the Latin word for "vinegar." Propionic acid is the smallest acid that shows some of the characteristics of the larger fatty acids (Section 20.1); its name comes from the Greek words *pro* ("the first") and *pion* ("fat"). Butyric acid is found in rancid butter; the Latin word for "butter" is *butyrum*. Valeric acid got its name from *valerian*, an herb that has been used as a sedative since Greco-Roman times. Caproic acid is found in goat's milk. If you have ever smelled a goat, then you know what caproic acid smells like. *Caper* is the Latin word for "goat."

In systematic nomenclature, the position of a substituent is designated by a number. The carbonyl carbon is always the C-1 carbon. In common nomenclature, the position of a substituent is designated by a lowercase Greek letter, and the carbonyl carbon is not given a designation. Thus, the carbon adjacent to the carbonyl carbon is the α-carbon, the carbon adjacent to the α-carbon is the β-carbon, and so on.

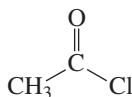
$$\underset{6}{CH_3}\underset{5}{CH_2}\underset{4}{CH_2}\underset{3}{CH_2}\underset{2}{CH_2}\underset{1}{C}(=O)OH \qquad \underset{\varepsilon}{CH_3}\underset{\delta}{CH_2}\underset{\gamma}{CH_2}\underset{\beta}{CH_2}\underset{\alpha}{CH_2}C(=O)OH$$

systematic nomenclature — common nomenclature

α = alpha
β = beta
γ = gamma
δ = delta
ε = epsilon

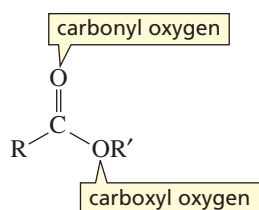
α-Hydroxycarboxylic acids are found in skin products that claim to reduce wrinkles by penetrating the top layer of the skin, causing it to flake off.

Take a careful look at the following examples to make sure that you understand the difference between systematic (IUPAC) and common nomenclature:

systematic name:	2-methoxybutanoic acid	3-bromopentanoic acid	4-chlorohexanoic acid
common name:	α-methoxybutyric acid	β-bromovaleric acid	γ-chlorocaproic acid

Naming Acyl Chlorides

Acyl chlorides have a Cl in place of the OH group of a carboxylic acid. Acyl chlorides are named by replacing “ic acid” of the acid name with “yl chloride.”

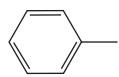
$CH_3C(=O)Cl$

systematic name:	ethanoyl chloride	3-methylpentanoyl chloride
common name:	acetyl chloride	β-methylvaleryl chloride

carbonyl oxygen

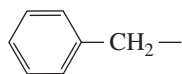
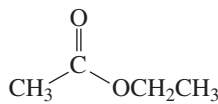
$RC(=O)OR'$

carboxyl oxygen

The double-bonded oxygen is the carbonyl oxygen; the single-bonded oxygen is the carboxyl oxygen.

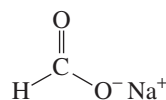
Naming Esters

An **ester** has an OR group in place of the OH group of a carboxylic acid. In naming an ester, the name of the group (R′) attached to the **carboxyl oxygen** is stated first, followed by the name of the acid, with “ic acid” replaced by “ate.” (The prime on R′ indicates that the alkyl group it designates does not have to be the same as the alkyl group designated by R.) Notice the difference between a phenyl group and a benzyl group.

a phenyl group

a benzyl group ($C_6H_5CH_2-$)

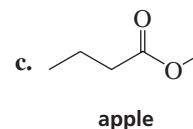
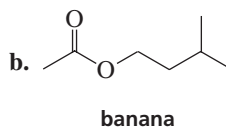
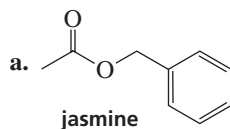
$CH_3C(=O)OCH_2CH_3$ $\quad$ $CH_3CH_2C(=O)OC_6H_5$ $\quad$ $CH_3CHBrCH_2C(=O)OCH_3$

systematic name:	ethyl ethanoate	phenyl propanoate	methyl 3-bromobutanoate
common name:	ethyl acetate	phenyl propionate	methyl β-bromobutyrate

Salts of carboxylic acids are named in the same way. That is, the cation is named first, followed by the name of the acid, again with “ic acid” replaced by “ate.”

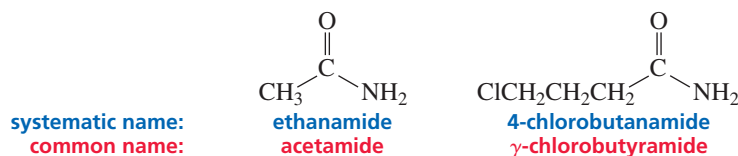
$HC(=O)O^- Na^+$ $\quad$ $CH_3C(=O)O^- K^+$

systematic name:	sodium methanoate	potassium ethanoate
common name:	sodium formate	potassium acetate

PROBLEM 1♦

The aromas of many flowers and fruits are due to esters such as those shown in this problem. What are the common names of these esters? (Also see Problem 41.)

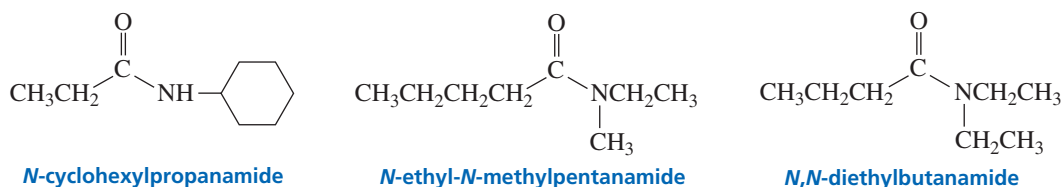
a. jasmine $\quad$ **b.** banana $\quad$ **c.** apple

Naming Amides

An **amide** has an NH_2, NHR, or NR_2 group in place of the OH group of a carboxylic acid. Amides are named by replacing "oic acid," "ic acid," or "ylic acid" of the acid name with "amide."

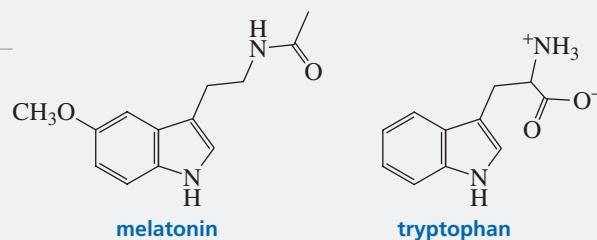
	$CH_3C(=O)NH_2$	$ClCH_2CH_2CH_2C(=O)NH_2$
systematic name:	ethanamide	4-chlorobutanamide
common name:	acetamide	γ-chlorobutyramide

If a substituent is bonded to the nitrogen, the name of the substituent is stated first (if there is more than one substituent bonded to the nitrogen, they are stated alphabetically), followed by the name of the amide. The name of each substituent is preceded by an *N* to indicate that the substituent is bonded to a nitrogen.

$CH_3CH_2C(=O)NH$–cyclohexyl
N-cyclohexylpropanamide

$CH_3CH_2CH_2CH_2C(=O)N(CH_3)CH_2CH_3$
N-ethyl-*N*-methylpentanamide

$CH_3CH_2CH_2C(=O)N(CH_2CH_3)CH_2CH_3$
N,N-diethylbutanamide

Nature's Sleeping Pill

Melatonin, a naturally occurring amide, is a hormone synthesized by the pineal gland from the amino acid tryptophan. An amino acid is an α-aminocarboxylic acid (Section 17.1). Melatonin regulates the dark–light clock in our brains that governs such things as the sleep–wake cycle, body temperature, and hormone production.

Melatonin levels increase from evening to night and then decrease as morning approaches. People with high levels of melatonin sleep longer and more soundly than those with low levels. The concentration of the hormone in our bodies varies with age—6-year-olds have more than five times the concentration that 80-year-olds have—which is one of the reasons young people have less trouble sleeping than older people. Melatonin supplements are used to treat insomnia, jet lag, and seasonal affective disorder.

PROBLEM 2♦

Name the following compounds:

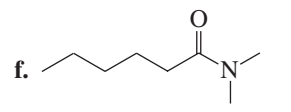
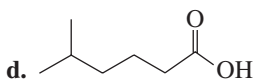
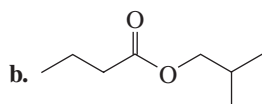
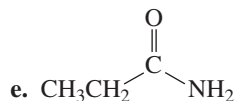
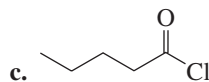
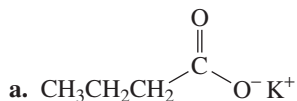
a. $CH_3CH_2CH_2C(=O)O^- K^+$

b. [skeletal structure]

c. [skeletal structure] Cl

d. [skeletal structure] OH

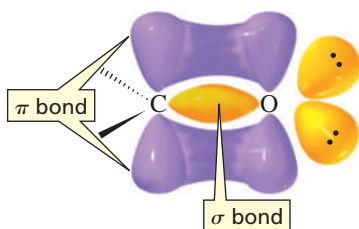
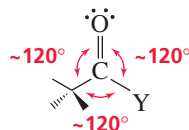
e. $CH_3CH_2C(=O)NH_2$

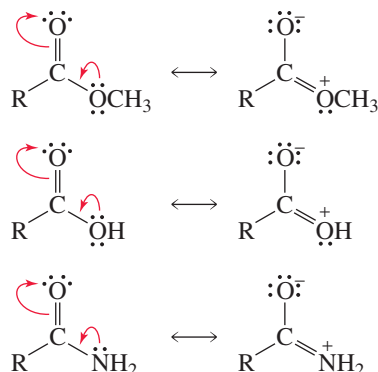
f. [skeletal structure] N

PROBLEM 3

Draw the structure for each of the following:

a. phenyl acetate
b. *N*-benzylethanamide
c. γ-methylcaproic acid
d. ethyl 2-chloropentanoate
e. β-bromobutyramide
f. α-chlorovaleric acid

11.2 THE STRUCTURES OF CARBOXYLIC ACIDS AND CARBOXYLIC ACID DERIVATIVES

The **carbonyl carbon** is sp^2 hybridized. It uses its three sp^2 orbitals to form σ bonds to the carbonyl oxygen, the α-carbon, and a substituent (Y). The three atoms attached to the carbonyl carbon are in the same plane, and the bond angles are each approximately 120°.

▲ **Figure 11.1**
Bonding in a carbonyl group. The π bond is formed by the side-to-side overlap of a *p* orbital of carbon with a *p* orbital of oxygen.

The **carbonyl oxygen** is also sp^2 hybridized. One of its sp^2 orbitals forms a σ bond with the carbonyl carbon, and each of the other two sp^2 orbitals contains a lone pair. The remaining *p* orbital of the carbonyl oxygen overlaps the remaining *p* orbital of the carbonyl carbon to form a π bond (Figure 11.1).

Esters, carboxylic acids, and amides each have two resonance contributors. The resonance contributor with separated charges (the one on the right) makes an insignificant contribution to the structure of an acyl chloride (Section 11.6), so it is not shown here.

The resonance contributor on the right makes a greater contribution to the hybrid in the amide than in the ester or the carboxylic acid, because the amide's resonance contributor is more stable. It is more stable because nitrogen is less electronegative than oxygen, so nitrogen can better accommodate a positive charge.

PROBLEM 4♦

Which is a correct statement?

A. The delocalization energy of an ester is about 18 kcal/mol, and the delocalization energy of an amide is about 10 kcal/mol.
B. The delocalization energy of an ester is about 10 kcal/mol, and the delocalization energy of an amide is about 18 kcal/mol.

PROBLEM 5♦

Which is longer: the carbon–oxygen single bond in a carboxylic acid or the carbon–oxygen bond in an alcohol? Why?

11.3 THE PHYSICAL PROPERTIES OF CARBONYL COMPOUNDS

The acid properties of carboxylic acids were discussed in Sections 2.3 and 7.8. Recall that carboxylic acids have pK_a values of approximately 5. Carbonyl compounds have the following relative boiling points:

relative boiling points

amide > carboxylic acid >> ester ~ acyl chloride ~ ketone ~ aldehyde

The boiling points of an ester, acyl chloride, ketone, and aldehyde of comparable molecular weight are similar and are *lower* than the boiling point of an alcohol of similar molecular weight, because only the alcohol molecules can form hydrogen bonds with each other. The boiling points of these four carbonyl compounds are *higher* than the boiling point of the same-sized ether because of the dipole–dipole interactions between the polar carbonyl groups.

$CH_3CH_2CH_2OH$ bp = 97.4 °C

$HCOOCH_3$ bp = 32 °C

CH_3COCl bp = 51 °C

CH_3COCH_3 bp = 56 °C

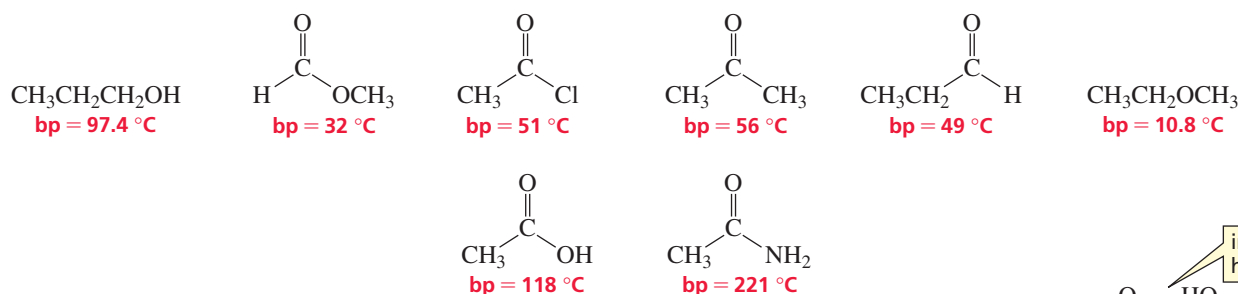
CH_3CH_2CHO bp = 49 °C

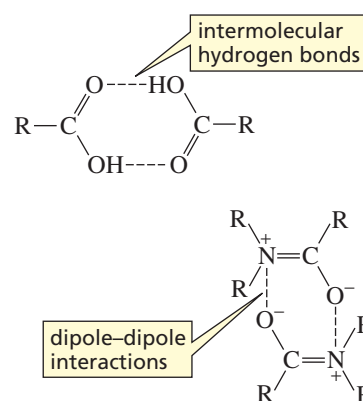
$CH_3CH_2OCH_3$ bp = 10.8 °C

CH_3COOH bp = 118 °C

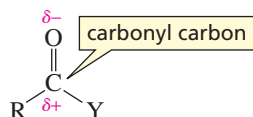
CH_3CONH_2 bp = 221 °C

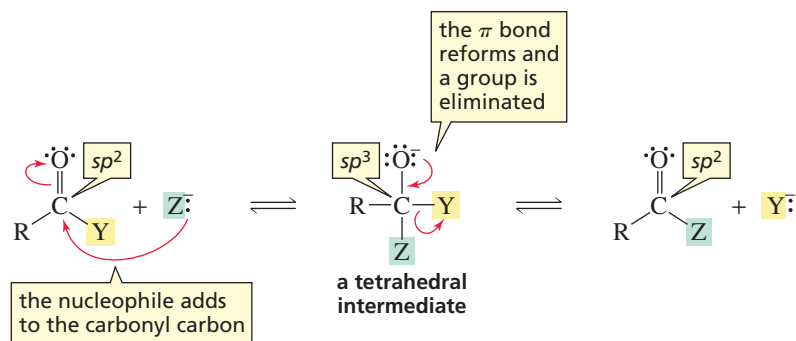
intermolecular hydrogen bonds

dipole–dipole interactions

Carboxylic acids have relatively high boiling points because each molecule has two groups that can form hydrogen bonds. Amides have the highest boiling points because they have strong dipole–dipole interactions, since the resonance contributor with separated charges contributes significantly to the overall structure of the compound (Section 11.2). In addition, if the nitrogen of an amide is bonded to a hydrogen, hydrogen bonds can form between the molecules.

Like alcohols and ethers, carbonyl compounds with fewer than four carbons are soluble in water. Tables of physical properties can be found in the Study Area of MasteringChemistry.

11.4 HOW CARBOXYLIC ACIDS AND CARBOXYLIC ACID DERIVATIVES REACT

The reactivity of carbonyl compounds is due to the polarity of the carbonyl group, which results from oxygen being more electronegative than carbon. The carbonyl carbon is, therefore, electron deficient (it is an electrophile), so it reacts with nucleophiles.

$R-C(=O^{\delta-})^{\delta+}-Y$ carbonyl carbon

When a nucleophile adds to the carbonyl carbon of a carboxylic acid derivative, the weakest bond in the molecule—the π bond—breaks, and an intermediate is formed. It is called a **tetrahedral intermediate** because the sp^2 carbon in the reactant has become an sp^3 carbon (that is, a tetrahedral carbon) in the intermediate.

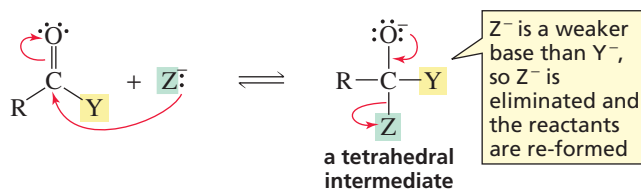
A compound that has an *sp*^{3} carbon bonded to an oxygen atom generally will be unstable if the *sp*^{3} carbon is bonded to another electronegative atom.

The tetrahedral compound is an intermediate rather than a final product because it is not stable. Generally, *a compound that has an* sp^3 *carbon bonded to an oxygen atom will be unstable if the* sp^3 *carbon is bonded to another electronegative atom*. The tetrahedral intermediate, therefore, is unstable because Y and Z are both electronegative atoms. A lone pair on the oxygen re-forms the π bond, and either Y^- or Z^- is eliminated along with its bonding electrons. (Here we show Y^- being eliminated.)

Whether Y^- or Z^- is eliminated from the tetrahedral intermediate depends on their relative basicities. The weaker base is eliminated preferentially, making this another example of the principle we first saw in Section 8.2: when comparing bases of the same type, we see that *the weaker base is a better leaving group*. Because a weak base does not share its electrons as well as a strong base does, a weaker base forms a weaker bond—one that is easier to break.

If Z^- is a weaker base than Y^-, then Z^- will be eliminated.

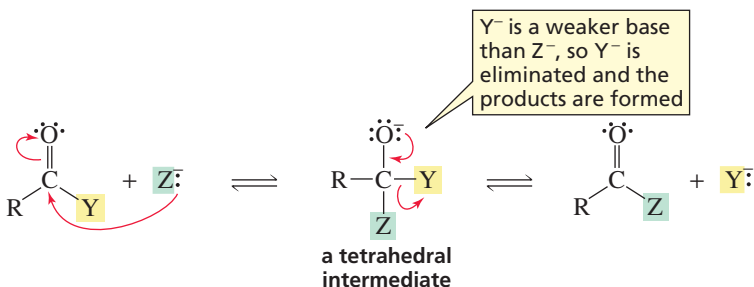
The weaker the base, the better it is as a leaving group.

Z^- is a weaker base than Y^-, so Z^- is eliminated and the reactants are re-formed

a tetrahedral intermediate

In this case, no new product is formed. The nucleophile adds to the carbonyl carbon, but the tetrahedral intermediate eliminates the nucleophile and re-forms the reactants.

On the other hand, if Y^- is a weaker base than Z^-, then Y^- will be eliminated and a new product will be formed.

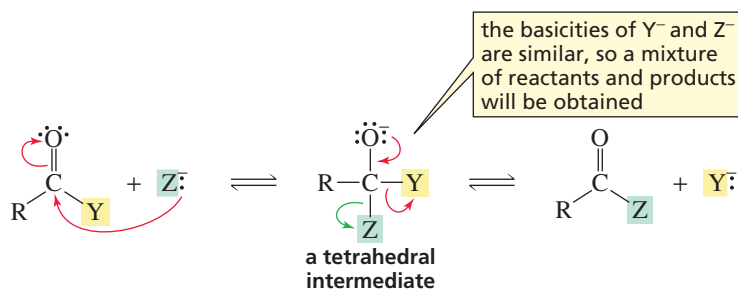
Y^- is a weaker base than Z^-, so Y^- is eliminated and the products are formed

a tetrahedral intermediate

This reaction is a **nucleophilic acyl substitution reaction** because a nucleophile (Z^-) has replaced the substituent (Y^-) that was attached to the acyl group in the reactant.

If the basicities of Y^- and Z^- are similar, some molecules of the tetrahedral intermediate will eliminate Y^- and others will eliminate Z^-. When the reaction is over, both the reactants and the products will be present.

the basicities of Y^- and Z^- are similar, so a mixture of reactants and products will be obtained

$$RC(=O)Y + Z:^- \rightleftharpoons R-C(O^-)(Z)-Y \rightleftharpoons RC(=O)Z + Y:^-$$

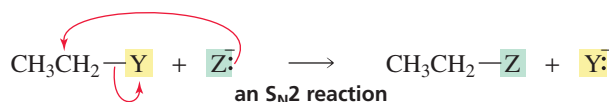
a tetrahedral intermediate

A carboxylic acid derivative will undergo a nucleophilic acyl substitution reaction if the newly added group in the tetrahedral intermediate is a stronger base than the group attached to the acyl group in the reactant.

We can therefore make the following general statement about the reactions of carboxylic acid derivatives:

A carboxylic acid derivative will undergo a nucleophilic acyl substitution reaction, provided that the newly added group in the tetrahedral intermediate is a stronger base than the group attached to the acyl group in the reactant.

Let's compare this two-step nucleophilic acyl substitution reaction with a one-step S_N2 reaction. When a nucleophile attacks a carbon, the weakest bond in the molecule breaks. The weakest bond in an S_N2 reaction is the bond to the leaving group, so this is the bond that breaks in the first and only step of the reaction (Section 8.1). In contrast, the weakest bond in a nucleophilic acyl substitution reaction is the π bond, so this bond breaks first and the leaving group is eliminated in a subsequent step.

$$CH_3CH_2-Y + Z:^- \longrightarrow CH_3CH_2-Z + Y:^-$$

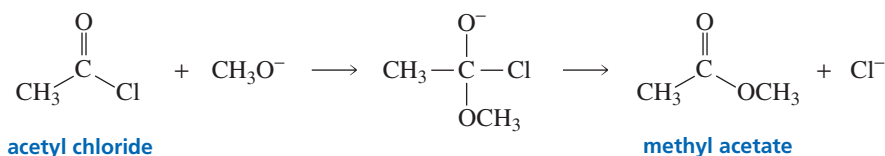
an S_N2 reaction

PROBLEM-SOLVING STRATEGY

Using Basicity to Predict the Outcome of a Nucleophilic Acyl Substitution Reaction

What is the product of the reaction of acetyl chloride with CH_3O^-? The pK_a of HCl is –7; the pK_a of CH_3OH is 15.5.

To identify the product of the reaction, we need to compare the basicities of the two groups in the tetrahedral intermediate so that we can determine which one will be eliminated. Because HCl is a stronger acid than CH_3OH, Cl^- is a weaker base than CH_3O^-. Therefore, Cl^- will be eliminated from the tetrahedral intermediate and methyl acetate will be the product of the reaction.

$$CH_3C(=O)Cl + CH_3O^- \longrightarrow CH_3-C(O^-)(OCH_3)-Cl \longrightarrow CH_3C(=O)OCH_3 + Cl^-$$

acetyl chloride — methyl acetate

Now use the strategy you have just learned to solve Problem 6.

PROBLEM 6♦

a. What is the product of the reaction of acetyl chloride with HO^-? The pK_a of HCl is –7; the pK_a of H_2O is 15.7.

b. What is the product of the reaction of acetamide with HO^-? The pK_a of NH_3 is 36; the pK_a of H_2O is 15.7.

PROBLEM 7♦

What will be the product of a nucleophilic acyl substitution reaction—a new carboxylic acid derivative, a mixture of two carboxylic acid derivatives, or no reaction—if the new group in the tetrahedral intermediate is

a. a stronger base than the substituent that was attached to the acyl group?

b. a weaker base than the substituent that was attached to the acyl group?

c. similar in basicity to the substituent that was attached to the acyl group?

11.5 THE RELATIVE REACTIVITIES OF CARBOXYLIC ACIDS AND CARBOXYLIC ACID DERIVATIVES

We have just seen that there are two steps in a nucleophilic acyl substitution reaction: *formation* of a tetrahedral intermediate and *collapse* of the tetrahedral intermediate. The weaker the base attached to the acyl group (Table 11.1), the easier it is for *both steps* of the reaction to take place. The relative basicities of the leaving groups are shown here.

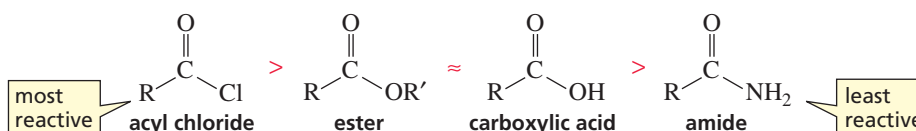
relative basicities of the leaving groups

weakest base $Cl^- < {}^-OR \approx {}^-OH < {}^-NH_2$ strongest base

Therefore, carboxylic acid derivatives have the following relative reactivities:

relative reactivities of carboxylic acid derivatives

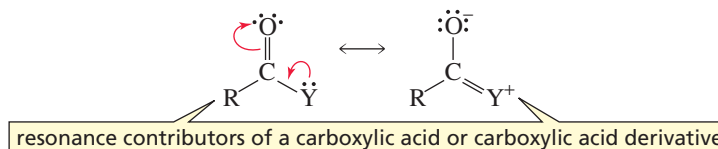
most reactive $RC(=O)Cl$ > $RC(=O)OR'$ ≈ $RC(=O)OH$ > $RC(=O)NH_2$ least reactive

acyl chloride > ester ≈ carboxylic acid > amide

How does having a weak base attached to the acyl group make the *first* step of the nucleophilic acyl substitution reaction easier? The key factor is the extent to which the lone pair electrons on Y can be delocalized onto the carbonyl oxygen.

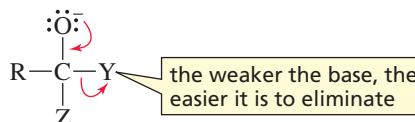
Weak bases do not share their electrons well, so the weaker the basicity of Y, the smaller will be the contribution from the resonance contributor with a positive charge on Y. In addition, when Y = Cl, delocalization of chlorine's lone pair is minimal due to the poor orbital overlap between the large 3*p* orbital on chlorine and the smaller 2*p* orbital on carbon. The less the contribution from the resonance contributor with the positive charge on Y, the more electrophilic the carbonyl carbon. Thus, weak bases cause the carbonyl carbon to be more electrophilic and, therefore, more reactive toward nucleophiles.

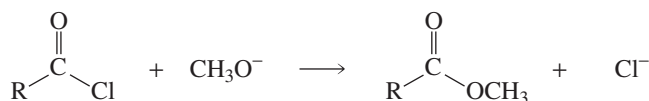
relative reactivity: acyl chloride > ester ~ carboxylic acid > amide

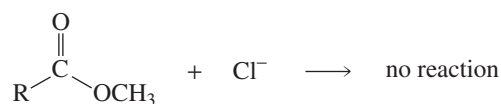
$RC(=O)\ddot{Y} \longleftrightarrow RC(-O^-)=Y^+$

resonance contributors of a carboxylic acid or carboxylic acid derivative

A weak base attached to the acyl group also makes the *second* step of the nucleophilic acyl substitution reaction easier, because weak bases are easier to eliminate when the tetrahedral intermediate collapses.

$R-C(O^-)(Z)-Y$

the weaker the base, the easier it is to eliminate

In Section 11.4 we saw that in a nucleophilic acyl substitution reaction, the nucleophile that adds to the carbonyl carbon must be a stronger base than the substituent that is attached to the acyl group. This means that *a carboxylic acid derivative can be converted into a less reactive carboxylic acid derivative in a nucleophilic acyl substitution reaction, but not into one that is more reactive*. For example, an acyl chloride can be converted into an ester, because an alkoxide ion is a stronger base than a chloride ion.

$$RC(=O)Cl + CH_3O^- \longrightarrow RC(=O)OCH_3 + Cl^-$$

An ester, however, cannot be converted into an acyl chloride because a chloride ion is a weaker base than an alkoxide ion.

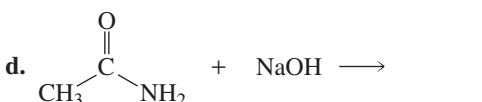
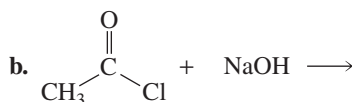
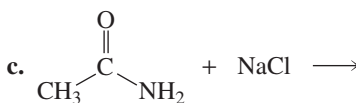
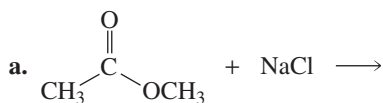
$$RC(=O)OCH_3 + Cl^- \longrightarrow \text{no reaction}$$

PROBLEM 8♦

Using the pK_a values listed in Table 11.1, predict the products of the following reactions:

a. $CH_3C(=O)OCH_3 + NaCl \longrightarrow$

b. $CH_3C(=O)Cl + NaOH \longrightarrow$

c. $CH_3C(=O)NH_2 + NaCl \longrightarrow$

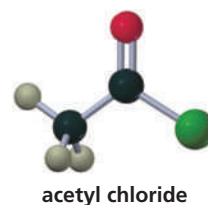
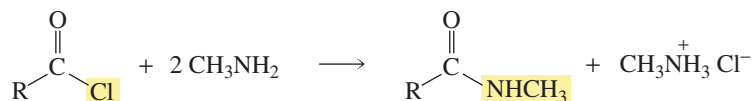
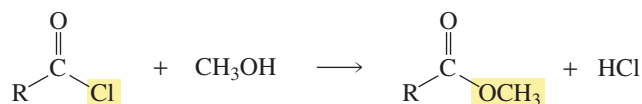
d. $CH_3C(=O)NH_2 + NaOH \longrightarrow$

11.6 THE REACTIONS OF ACYL CHLORIDES

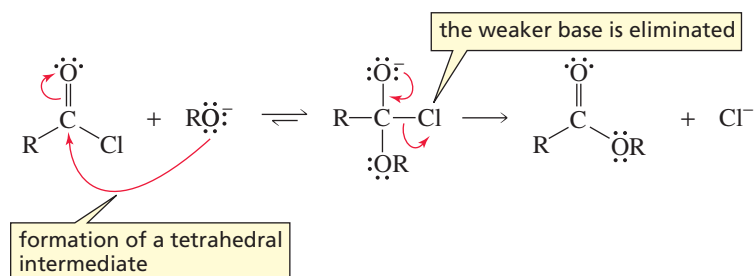
Acyl chlorides react with alcohols to form esters, with water to form carboxylic acids, and with amines to form amides because, in each case, the incoming nucleophile is a stronger base than the departing halide ion (Table 11.1).

acetyl chloride

$$RC(=O)Cl + CH_3OH \longrightarrow RC(=O)OCH_3 + HCl$$

$$RC(=O)Cl + H_2O \longrightarrow RC(=O)OH + HCl$$

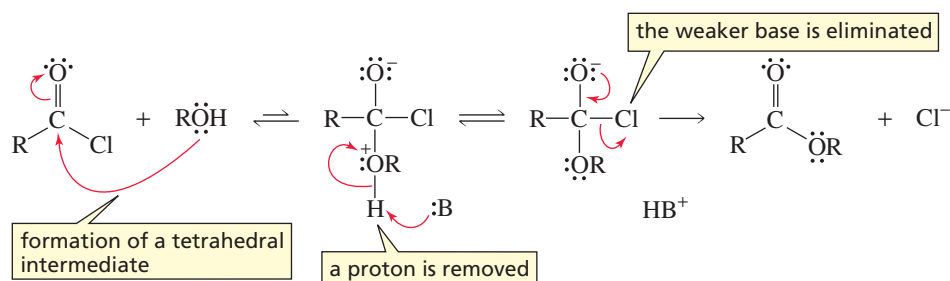
$$RC(=O)Cl + 2\,CH_3NH_2 \longrightarrow RC(=O)NHCH_3 + CH_3\overset{+}{N}H_3\,Cl^-$$

All carboxylic acid derivatives undergo nucleophilic acyl substitution reactions by one of the two following mechanisms. The mechanism followed depends on whether the nucleophile is charged or neutral.

MECHANISM FOR THE REACTION OF AN ACYL CHLORIDE WITH A NEGATIVELY CHARGED NUCLEOPHILE

The weaker base is eliminated from the tetrahedral intermediate.

- The nucleophile adds to the carbonyl carbon, forming a tetrahedral intermediate.
- The unstable tetrahedral intermediate collapses, eliminating the chloride ion because it is a weaker base than the alkoxide ion.

If the nucleophile is neutral, the mechanism has an additional step in which a proton is lost.

MECHANISM FOR THE REACTION OF AN ACYL CHLORIDE WITH A NEUTRAL NUCLEOPHILE

The weaker base is eliminated from the tetrahedral intermediate.

the weaker base is eliminated

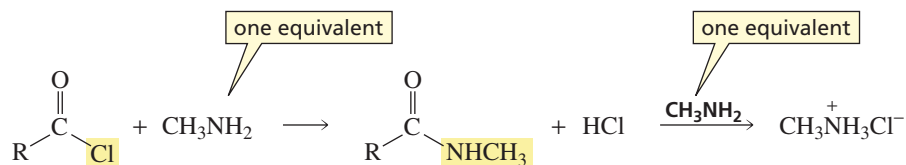
formation of a tetrahedral intermediate

a proton is removed

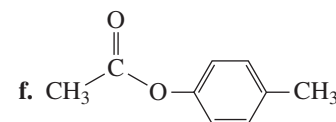
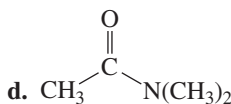
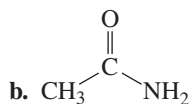
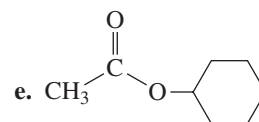
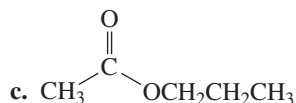
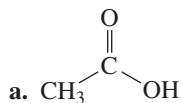
HB^+ + Cl^-

- The nucleophile adds to the carbonyl carbon, forming a tetrahedral intermediate.
- Because the protonated ether group is a strong acid, the tetrahedral intermediate loses a proton. (:B represents any species in the solution that can remove a proton.)
- The unstable tetrahedral intermediate collapses, eliminating the chloride ion because it is a weaker base than the alkoxide ion.

Notice that the reaction of an acyl chloride with an amine, on the previous page, to form an amide is carried out with twice as much amine as acyl chloride, because the HCl formed as a product of the reaction will protonate any amine that has yet to react. Once protonated, it is no longer a nucleophile, so it cannot react with the acyl chloride. Using twice as much amine as acyl chloride guarantees that there will be enough unprotonated amine to react with all the acyl chloride.

$RCOCl + CH_3NH_2$ (one equivalent) $\longrightarrow RCONHCH_3 + HCl \xrightarrow{CH_3NH_2} CH_3\overset{+}{N}H_3Cl^-$ (one equivalent)

PROBLEM 9

Starting with acetyl chloride, what neutral nucleophile would you use to make each of the following compounds?

a. CH_3COOH
b. CH_3CONH_2
c. $CH_3COOCH_2CH_2CH_3$
d. $CH_3CON(CH_3)_2$
e. CH_3CO–O–cyclohexyl
f. CH_3CO–O–C_6H_4–CH_3

PROBLEM 10

Write the mechanism for each of the following reactions:

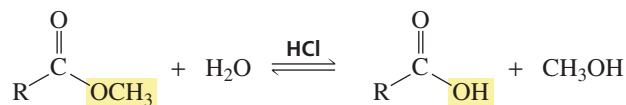
a. the reaction of acetyl chloride with water to form acetic acid
b. the reaction of acetyl chloride with excess methylamine to form *N*-methylacetamide

11.7 THE REACTIONS OF ESTERS

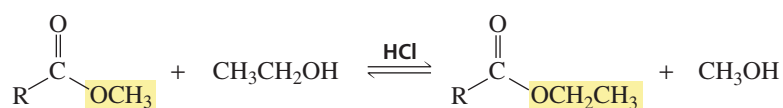
Esters do not react with chloride ion because it is a much weaker base than the RO^- group of the ester, so Cl^- (not RO^-) would be the base eliminated from the tetrahedral intermediate (Table 11.1).

An ester reacts with water to form a carboxylic acid and an alcohol. This is an example of a hydrolysis reaction. A **hydrolysis reaction** is a reaction with water that converts one compound into two compounds (*lysis* is Greek for "breaking down").

a hydrolysis reaction

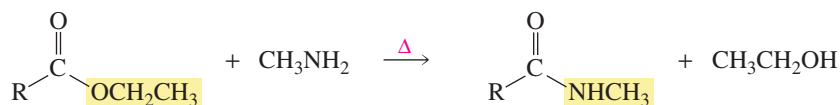
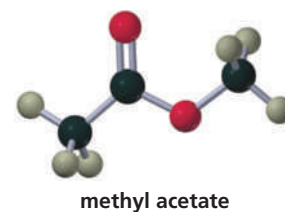
$$\mathrm{RC(=O)OCH_3 + H_2O \xrightleftharpoons{\text{HCl}} RC(=O)OH + CH_3OH}$$

An ester reacts with an alcohol to form a new ester and a new alcohol. This is an example of an **alcoholysis reaction**—a reaction with an alcohol that converts one compound into two compounds. This particular alcoholysis reaction is also called a **transesterification reaction** because one ester is converted to another ester.

a transesterification reaction

$$\mathrm{RC(=O)OCH_3 + CH_3CH_2OH \xrightleftharpoons{\text{HCl}} RC(=O)OCH_2CH_3 + CH_3OH}$$

Both the hydrolysis and the transesterification of an ester are very slow reactions, because water and alcohols are poor nucleophiles and the RO^- group of an ester is a poor leaving group. Therefore, these reactions are always catalyzed when carried out in the laboratory. Both hydrolysis and transesterification of an ester can be catalyzed by acids (Section 11.8). The rate of hydrolysis can also be increased by hydroxide ion and the rate of transesterification can be increased by the conjugate base (RO^-) of the reactant alcohol (Section 11.9).

Esters react with amines to form amides. A reaction with an amine that converts one compound into two compounds is called **aminolysis.** Notice that the aminolysis of an ester requires only one equivalent of amine, unlike the aminolysis of an acyl halide, which requires two equivalents (Section 11.6). This is because the leaving group of an ester (RO^-) is more basic than the amine, so the alkoxide ion—rather than unreacted amine—picks up the proton generated in the reaction.

an aminolysis reaction

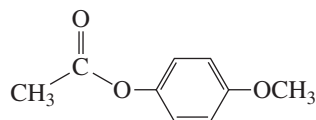
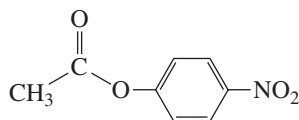
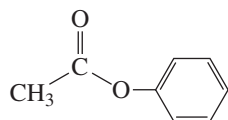
$$\mathrm{RC(=O)OCH_2CH_3 + CH_3NH_2 \xrightarrow{\Delta} RC(=O)NHCH_3 + CH_3CH_2OH}$$

The reaction of an ester with an amine is not as slow as the reaction of an ester with water or an alcohol because an amine is a better nucleophile. This is fortunate because the reaction cannot be catalyzed by an acid. The acid would protonate the amine, and a protonated amine is not a nucleophile. The rate of the reaction, however, can be increased by heat.

PROBLEM 11

Write a mechanism for each of the following reactions:

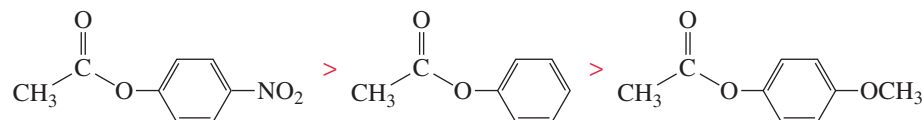
a. the noncatalyzed hydrolysis of methyl propionate.
b. the aminolysis of phenyl formate, using methylamine.

PROBLEM 12 Solved

List the following esters in order from most reactive to least reactive toward hydrolysis:

$\mathrm{CH_3C(=O)O{-}C_6H_5}$ $\quad$ $\mathrm{CH_3C(=O)O{-}C_6H_4{-}NO_2}$ $\quad$ $\mathrm{CH_3C(=O)O{-}C_6H_4{-}OCH_3}$

Solution We know that the reactivity of a carboxylic acid derivative depends on the basicity of the group attached to the acyl group—the weaker the base, the easier it is for *both steps* of the reaction to take place (Section 11.5). So now we need to compare the basicities of the three phenolate ions.

The nitro-substituted phenolate ion is the weakest base because the nitro group withdraws electrons inductively and by resonance (Section 7.9), which decreases the concentration of negative charge on the oxygen. The methoxy-substituted phenolate ion is the strongest base because the methoxy group donates electrons by resonance more than it withdraws electrons inductively (Section 7.9), so the concentration of negative charge on the oxygen is increased. Therefore, the three esters have the following relative reactivity toward hydrolysis:

$CH_3C(=O)O\text{–}C_6H_4\text{–}NO_2$ > $CH_3C(=O)O\text{–}C_6H_5$ > $CH_3C(=O)O\text{–}C_6H_4\text{–}OCH_3$

11.8 ACID-CATALYZED ESTER HYDROLYSIS AND TRANSESTERIFICATION

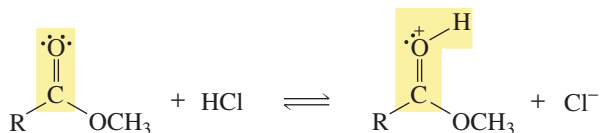
We have seen that esters hydrolyze slowly because water is a poor nucleophile and esters have relatively basic leaving groups. The rate of hydrolysis can be increased by either acid or hydroxide ion. When you examine the mechanisms for these reactions, notice the following features that hold for all organic reactions:

All organic intermediates and products in acidic solutions are positively charged or neutral; negatively charged organic intermediates and products are not formed in acidic solutions.

All organic intermediates and products in basic solutions are negatively charged or neutral; positively charged organic intermediates and products are not formed in basic solutions.

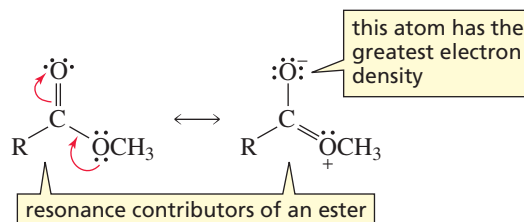
When an acid is added to a reaction, the *first thing* that happens is the acid protonates the most basic atom in the reactant—that is, the one with the greatest electron density. Therefore, when an acid is added to an ester, the acid protonates the carbonyl oxygen.

When an acid is added to a reaction, it protonates the most basic atom in the reactant.

$$RC(=O)OCH_3 + HCl \rightleftharpoons RC(=\overset{+}{O}H)OCH_3 + Cl^-$$

The resonance contributors of the ester show why the carbonyl oxygen is the atom with the greatest electron density.

$$RC(=O)\ddot{O}CH_3 \longleftrightarrow RC(\text{–}O^-)=\overset{+}{O}CH_3$$

this atom has the greatest electron density

resonance contributors of an ester

The mechanism for the acid-catalyzed hydrolysis of an ester is shown next. (HB^+ represents any species in the solution that is capable of donating a proton and :B represents any species that is capable of removing a proton.)

MECHANISM FOR ACID-CATALYZED ESTER HYDROLYSIS

the acid protonates the carbonyl oxygen

the nucleophile adds to the carbonyl carbon

tetrahedral intermediate I

equilibration of the 3 tetrahedral intermediates; either OH or OCH_3 can be protonated

tetrahedral intermediate II

removal of a proton from the carbonyl oxygen

elimination of the weaker base

tetrahedral intermediate III

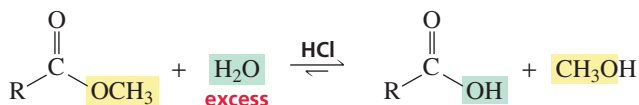
Pay attention to the three tetrahedral intermediates that occur in this mechanism:

protonated tetrahedral intermediate I ⇌ neutral tetrahedral intermediate II ⇌ protonated tetrahedral intermediate III.

This pattern will be repeated in many more acid-catalyzed reactions.

- The acid protonates the carbonyl oxygen.
- The nucleophile (H_2O) adds to the carbonyl carbon of the protonated carbonyl group, forming a protonated tetrahedral intermediate.
- The protonated tetrahedral intermediate (I) is in equilibrium with its nonprotonated form (II).
- The nonprotonated tetrahedral intermediate can be re-protonated on OH, which re-forms tetrahedral intermediate I, or it can be protonated on OCH_3, which forms tetrahedral intermediate III. (From Section 2.10, we know that the relative amounts of the three tetrahedral intermediates depend on the pH of the solution and the pK_a values of the protonated intermediates.)
- When tetrahedral intermediate I collapses, it eliminates H_2O in preference to CH_3O^- (because H_2O is a weaker base), and re-forms the ester. When tetrahedral intermediate III collapses, it eliminates CH_3OH rather than HO^- (because CH_3OH is a weaker base) and forms the carboxylic acid. Because H_2O and CH_3OH have approximately the same basicity, it will be as likely for tetrahedral intermediate I to collapse to re-form the ester as it will for tetrahedral intermediate III to collapse to form the carboxylic acid. (Tetrahedral intermediate II is much less likely to collapse because both HO^- and CH_3O^- are strong bases and, therefore, poor leaving groups.)
- Removal of a proton from the protonated carboxylic acid forms the carboxylic acid and re-forms the acid catalyst.

Because tetrahedral intermediates I and III are equally likely to collapse, both ester and carboxylic acid will be present when the reaction has reached equilibrium. Excess water can be used to force the equilibrium to the right (Le Châtelier's principle; Section 5.5). Or, if the boiling point of the product alcohol is significantly lower than the boiling points of the other components of the reaction, the reaction can be driven to the right by distilling off the alcohol as it is formed.

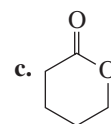
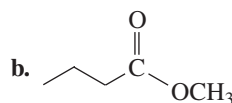
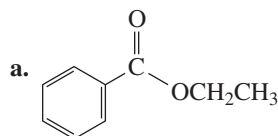
$$RCOOCH_3 + H_2O \text{ (excess)} \overset{HCl}{\rightleftharpoons} RCOOH + CH_3OH$$

The mechanism for the reverse reaction, the acid-catalyzed reaction of a carboxylic acid and an alcohol to form an ester and water, is the exact reverse of the mechanism for the acid-catalyzed hydrolysis of an ester to form a carboxylic acid and an alcohol.

PROBLEM 13

What products would be formed from the acid-catalyzed hydrolysis of the following esters?

a. $C_6H_5C(=O)OCH_2CH_3$

b. $CH_3CH_2CH_2C(=O)OCH_3$

c. (six-membered cyclic ester)

PROBLEM 14

Using the mechanism for the acid-catalyzed hydrolysis of an ester as your guide, write the mechanism—showing all the curved arrows—for the acid-catalyzed reaction of acetic acid and methanol to form methyl acetate. Use HB^+ and :B to represent the proton-donating and proton-removing species, respectively.

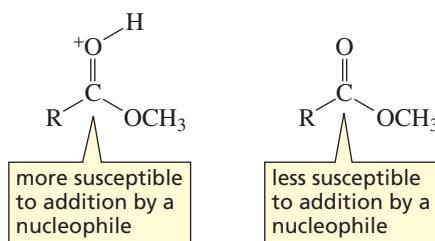
Now let's see how the acid catalyst increases the rate of ester hydrolysis. For a catalyst to increase the rate of a reaction, it must increase the rate of the slow step of the reaction, because changing the rate of a fast step will not affect the rate of the overall reaction. Four of the six steps in the mechanism for acid-catalyzed ester hydrolysis are proton-transfer steps. Proton transfer to or from an electronegative atom such as oxygen or nitrogen is always a fast step. The other two steps in the mechanism—namely, formation of the tetrahedral intermediate and collapse of the tetrahedral intermediate—are relatively slow. The acid increases the rates of both these steps.

The acid increases *the rate of formation of the tetrahedral intermediate* by protonating the carbonyl oxygen. Protonated carbonyl groups are more susceptible than nonprotonated carbonyl groups to nucleophilic addition, because a positively charged oxygen is more electron withdrawing than an uncharged oxygen. Increased electron withdrawal by the positively charged oxygen makes the carbonyl carbon more electron deficient, which increases its reactivity toward nucleophiles.

An acid catalyst increases the reactivity of a carbonyl group.

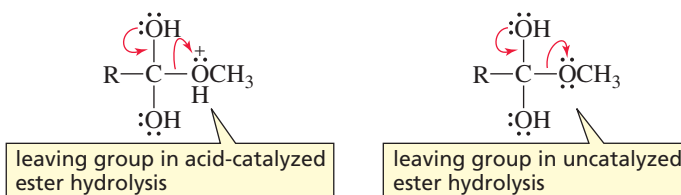
protonation of the carbonyl oxygen increases the susceptibility of the carbonyl carbon to nucleophilic addition

$R-C(=\overset{+}{O}H)-OCH_3$ — more susceptible to addition by a nucleophile

$R-C(=O)-OCH_3$ — less susceptible to addition by a nucleophile

The acid increases *the rate of collapse of the tetrahedral intermediate* by decreasing the basicity of the leaving group, which makes it easier to eliminate: in the acid-catalyzed hydrolysis of an ester, the leaving group is CH_3OH, which is a weaker base than CH_3O^-, the leaving group in the uncatalyzed reaction.

An acid catalyst increases the leaving propensity of a group.

$R-C(OH)(OH)-\overset{+}{O}(H)CH_3$ — leaving group in acid-catalyzed ester hydrolysis

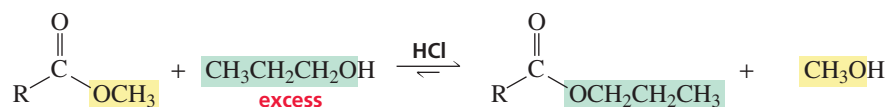
$R-C(OH)(OH)-OCH_3$ — leaving group in uncatalyzed ester hydrolysis

PROBLEM 15

In the mechanism for the acid-catalyzed hydrolysis of an ester,

a. what species could be represented by HB^+?
b. what species could be represented by :B?
c. what species is HB^+ most likely to be in the hydrolysis reaction?
d. what species is HB^+ most likely to be in the reverse reaction?

Transesterification

Transesterification—the reaction of an ester with an alcohol—is also catalyzed by acid. The mechanism for acid-catalyzed transesterification is identical to the mechanism for acid-catalyzed ester hydrolysis, except that the nucleophile is ROH rather than H_2O. As in ester hydrolysis, the leaving groups in the tetrahedral intermediate have approximately the same basicity. Consequently, an excess of the reactant alcohol must be used to produce a good yield of the desired product.

$$RC(=O)OCH_3 + \underset{\text{excess}}{CH_3CH_2CH_2OH} \underset{}{\overset{HCl}{\rightleftharpoons}} RC(=O)OCH_2CH_2CH_3 + CH_3OH$$

PROBLEM 16♦

What products would be obtained from the following reactions?

a. ethyl butyrate + excess isopropanol + HCl **b.** phenyl acetate + excess ethanol + HCl

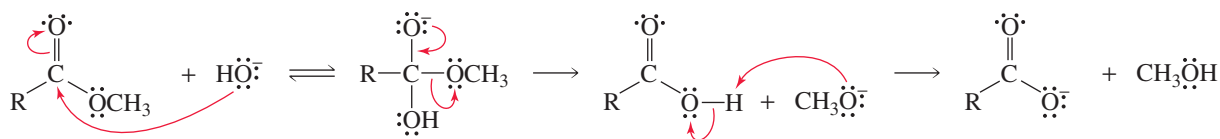
PROBLEM 17

Write the mechanism for the acid-catalyzed transesterification of ethyl acetate with methanol.

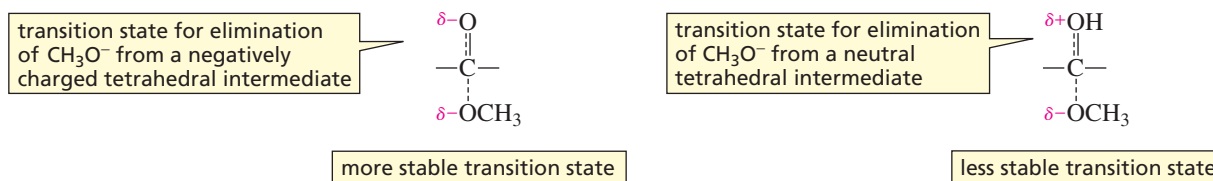
11.9 HYDROXIDE-ION-PROMOTED ESTER HYDROLYSIS

The rate of hydrolysis of an ester can be increased by hydroxide ion. Like an acid catalyst, hydroxide ion increases the rates of the two slow steps of the reaction—namely, formation of the tetrahedral intermediate and collapse of the tetrahedral intermediate.

MECHANISM FOR THE HYDROXIDE-ION-PROMOTED HYDROLYSIS OF AN ESTER

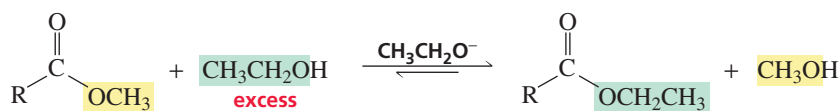
$$RC(=O)OCH_3 + HO^- \rightleftharpoons R-C(O^-)(OH)-OCH_3 \longrightarrow RC(=O)O-H + CH_3O^- \longrightarrow RC(=O)O^- + CH_3OH$$

- Hydroxide ion adds to the carbonyl carbon of the ester.
- The two potential leaving groups in the tetrahedral intermediate (HO^- and CH_3O^-) have the same leaving propensity. Elimination of HO^- re-forms the ester, whereas elimination of CH_3O^- forms a carboxylic acid.
- The final products are not the carboxylic acid and methoxide ion, because if only one base is protonated, it will be the stronger base. Therefore, the final products are the carboxylate ion and methanol because CH_3O^- is more basic than $RCOO^-$. The reaction is irreversible because the negatively charged carboxylate ion cannot be approached by a nucleophile.

Hydroxide ion increases the rate of formation of the tetrahedral intermediate because HO^- is a better nucleophile than H_2O. Hydroxide ion increases the rate of collapse of the tetrahedral intermediate, because in a basic solution the tetrahedral intermediate is negatively charged. The transition state for expulsion of CH_3O^- by a negatively charged oxygen is more stable than the transition state for expulsion of CH_3O^- by a neutral oxygen since, in the former, the oxygen does not develop a partial positive charge.

Hydroxide ion is a better nucleophile than water.

The hydrolysis of an ester in the presence of hydroxide ion is called a *hydroxide-ion-promoted reaction* rather than a base-catalyzed reaction, because hydroxide ion increases the rate of the first step of the reaction by being a better nucleophile than water—not by being a stronger base than water—and because hydroxide ion is consumed in the overall reaction. To be a catalyst, a species must not be changed by or consumed in the reaction (Section 5.10). Therefore, the reaction must be carried out with an equivalent of hydroxide ion, not a catalytic amount.

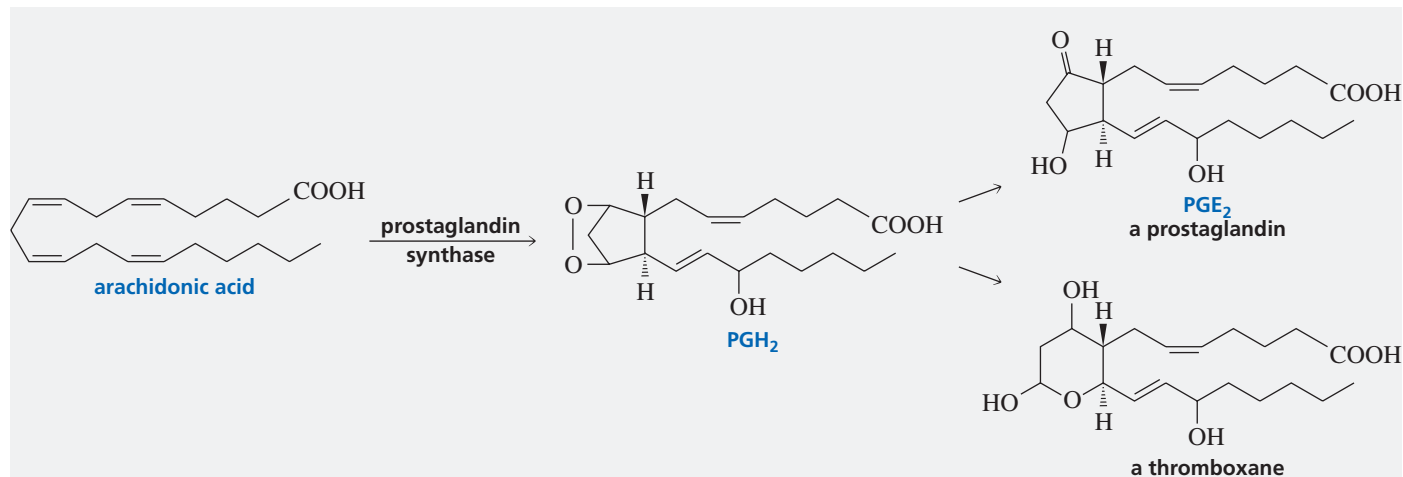
Hydroxide ion promotes only hydrolysis reactions. Hydroxide ion cannot promote reactions of carboxylic acid derivatives with alcohols or with amines, because one function of the hydroxide ion is to provide a good nucleophile for the first step of the reaction. When the nucleophile is an alcohol or an amine, nucleophilic addition by hydroxide ion would form a different product from the one that would be formed by the alcohol or amine. Hydroxide can be used to promote a hydrolysis reaction because the same product is formed, whether the nucleophile that adds to the carbonyl carbon is H_2O or HO^-.

Reactions in which the nucleophile is an alcohol can be promoted by the conjugate base of the alcohol. The function of the alkoxide ion is to provide a good nucleophile for the reaction, so only reactions in which the nucleophile is an alcohol can be promoted by the conjugate base of the alcohol.

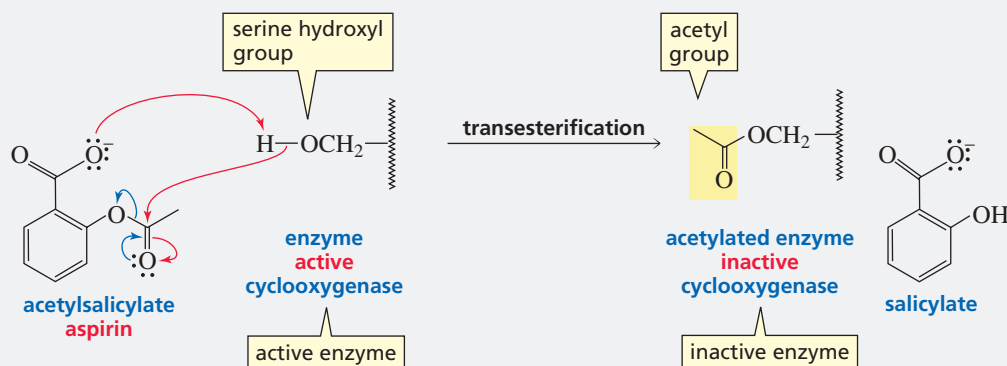
$$RC(=O)OCH_3 + \underset{\text{excess}}{CH_3CH_2OH} \underset{}{\overset{CH_3CH_2O^-}{\rightleftharpoons}} RC(=O)OCH_2CH_3 + CH_3OH$$

Aspirin, NSAIDs, and COX-2 Inhibitors

Salicylic acid, found in willow bark and myrtle leaves, is perhaps the oldest known drug. As early as the fifth century B.C., Hippocrates wrote about the curative powers of willow bark. In 1897, scientists working at Bayer and Co. a drug and dye firm in Germany (see page 129), found that acylating salicylic acid produced a more potent drug to control fever and pain (see page 122). Bayer called it *aspirin*: "a" was for acetyl, "spir" was for the spiraea flower that also contains salicylic acid, and "in" was a common ending for drug names at that time. It soon became the world's best-selling drug. However, its mode of action was not discovered until 1971, when it was found that the anti-inflammatory and fever-reducing activity of aspirin was due to a transesterification reaction that blocks the synthesis of prostaglandins.

Prostaglandins have several different physiological functions (Section 20.6). One is to stimulate inflammation and another to induce fever. The enzyme prostaglandin synthase catalyzes the conversion of arachidonic acid, a naturally occurring carboxylic acid (see Table 20.1), into PGH_2, the precursor of all prostaglandins and the related thromboxanes.

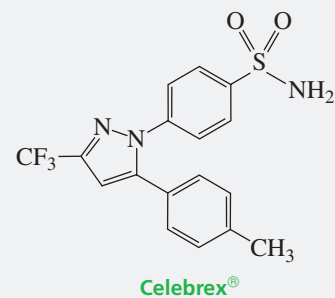
arachidonic acid → (prostaglandin synthase) → PGH_2 → PGE_2 a prostaglandin; a thromboxane

Prostaglandin synthase is composed of two enzymes. One of them—cyclooxygenase—has a CH_2OH group at its active site that is necessary for enzymatic activity. When the CH_2OH group reacts with aspirin in a transesterification reaction, the enzyme is inactivated. This prevents prostaglandins from being synthesized, so inflammation is suppressed and fever is reduced. Notice that the carboxyl group of aspirin is a basic catalyst. It removes a proton from the CH_2OH group, which makes it a better nucleophile. This is why aspirin is maximally active in its basic form (see page 88). (The red arrows show the formation of the tetrahedral intermediate; the blue arrows show its collapse.)

serine hydroxyl group; acetyl group

acetylsalicylate aspirin + enzyme active cyclooxygenase (active enzyme) → (transesterification) → acetylated enzyme inactive cyclooxygenase (inactive enzyme) + salicylate

Because aspirin inhibits the formation of PGH_2, it also inhibits the synthesis of thromboxanes, the compounds involved in blood clotting. Presumably, this is why low levels of aspirin have been reported to reduce the incidence of strokes and heart attacks that result from the formation of blood clots. Because of aspirin's activity as an anticoagulant, doctors caution patients not to take aspirin for several days before surgery.

Other NSAIDs (nonsteroidal anti-inflammatory drugs), such as ibuprofen (the active ingredient in Advil, Motrin, and Nuprin) and naproxen (the active ingredient in Aleve), also inhibit the synthesis of prostaglandins.

There are two forms of prostaglandin synthase: one carries out the normal production of prostaglandin, and the other synthesizes additional prostaglandin in response to inflammation. NSAIDs inhibit the synthesis of all prostaglandins. One prostaglandin regulates the production of acid in the stomach, so when prostaglandin synthesis stops, the acidity of the stomach can rise above normal levels. Celebrex, a relatively new drug, inhibits only the prostaglandin synthase that produces prostaglandin in response to inflammation. Thus, inflammatory conditions now can be treated without some of the harmful side effects.

Celebrex®

PROBLEM 18♦

a. What species other than an acid can be used to increase the rate of the transesterification reaction that converts methyl acetate to propyl acetate?

b. Explain why the rate of aminolysis of an ester cannot be increased by H^+, HO^-, or RO^-.

PROBLEM 19 Solved

Early chemists could envision three possible mechanisms for hydroxide-ion-promoted ester hydrolysis. Devise an experiment that would show which of the three is the actual mechanism.

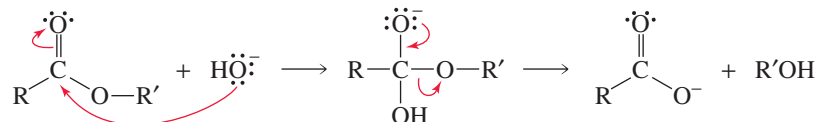
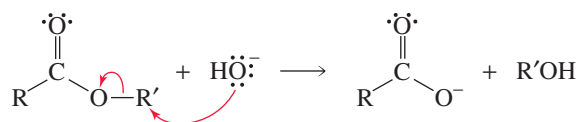
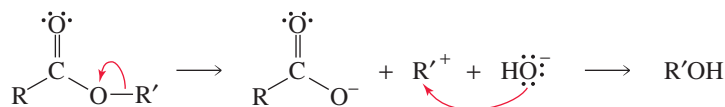
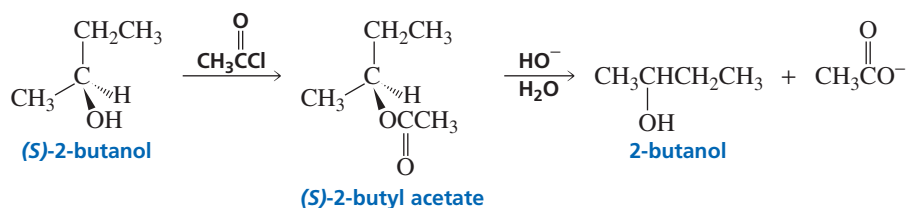
1. a nucleophilic acyl substitution reaction

$$RC(=O)OR' + HO^- \longrightarrow R{-}C(O^-)(OH){-}OR' \longrightarrow RC(=O)O^- + R'OH$$

2. an S_N2 reaction

$$RC(=O)O{-}R' + HO^- \longrightarrow RC(=O)O^- + R'OH$$

3. an S_N1 reaction

$$RC(=O)O{-}R' \longrightarrow RC(=O)O^- + R'^+ + HO^- \longrightarrow R'OH$$

Solution Start with a single stereoisomer of an alcohol with the OH group bonded to an asymmetric center and determine its specific rotation. Then convert the alcohol into an ester using an acyl chloride such as acetyl chloride. Next, hydrolyze the ester under basic conditions, isolate the alcohol (2-butanol) obtained as a product, and determine its specific rotation.

$$\underset{\textit{(S)}\text{-2-butanol}}{CH_3CH(OH)CH_2CH_3} \xrightarrow{CH_3CCl\ (\text{O})} \underset{\textit{(S)}\text{-2-butyl acetate}}{CH_3CH(OCCH_3)CH_2CH_3} \xrightarrow[H_2O]{HO^-} \underset{\text{2-butanol}}{CH_3CH(OH)CH_2CH_3} + CH_3CO^-$$

If the reaction is a nucleophilic acyl substitution reaction, the product alcohol will have the same specific rotation as the reactant alcohol, because no bonds to the asymmetric center are broken during the formation or hydrolysis of the ester.

If the reaction is an S_N2 reaction, the product alcohol and the reactant alcohol will have opposite specific rotations, because the mechanism requires back-side attack of hydroxide ion on the asymmetric center (Section 8.1).

If the reaction is an S_N1 reaction, the product alcohol will have a small (or zero) specific rotation, because the mechanism requires carbocation formation, which leads to formation of both the *R* and *S* stereoisomers of the alcohol in approximately equal amounts (Section 8.3).

11.10 REACTIONS OF CARBOXYLIC ACIDS

acetic acid

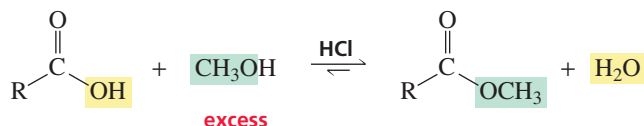
Carboxylic acids can undergo nucleophilic acyl substitution reactions only when they are in their acidic forms. The basic form of a carboxylic acid is not reactive because its negative charge makes it resistant to approach by a nucleophile. Therefore, carboxylate ions are even less reactive than amides in nucleophilic acyl substitution reactions.

relative reactivities toward nucleophilic acyl substitution

most reactive $RC(=O)OH > RC(=O)NH_2 > RC(=O)O^-$ least reactive

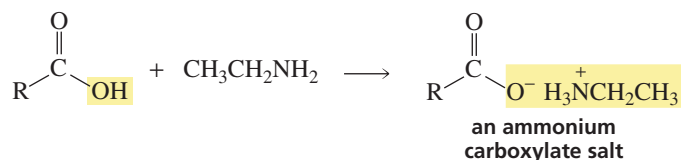
Carboxylic acids have approximately the same reactivity as esters, because the HO^- leaving group of a carboxylic acid has about the same basicity as the RO^- leaving group of an ester.

Carboxylic acids, therefore, react with alcohols to form esters. The reaction must be carried out in an acidic solution, not only to catalyze the reaction but also to keep the carboxylic acid in its acidic form so that the nucleophile will react with it. Because the tetrahedral intermediate formed in this reaction has two potential leaving groups with approximately the same basicity, the reaction must be carried out with excess alcohol to drive it toward products.

$$\text{RCOOH} + \underset{\text{excess}}{CH_3OH} \underset{}{\overset{\text{HCl}}{\rightleftharpoons}} \text{RCOOCH}_3 + H_2O$$

The mechanism of the reaction is the exact reverse of the mechanism for the acid-catalyzed hydrolysis of an ester shown on page 435. Also see Problem 14.

Carboxylic acids do not undergo nucleophilic acyl substitution reactions with amines. A carboxylic acid is an acid and an amine is a base, so the carboxylic acid immediately loses a proton to the amine when the two compounds are mixed. The resulting ammonium carboxylate salt is the final product of the reaction; the carboxylate ion is not reactive and the protonated amine is not a nucleophile.

$$\text{RCOOH} + CH_3CH_2NH_2 \longrightarrow \text{RCOO}^-\ H_3\overset{+}{N}CH_2CH_3$$

an ammonium carboxylate salt

PROBLEM 20♦

Show how each of the following esters could be prepared using a carboxylic acid as one of the starting materials:

a. methyl butyrate (odor of apples) **b.** octyl acetate (odor of oranges)

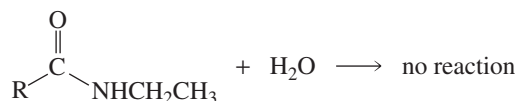
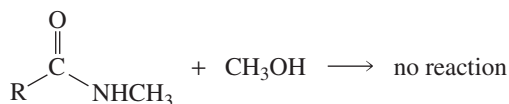
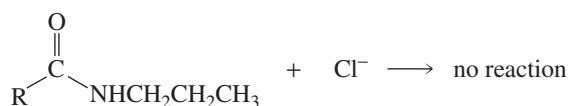
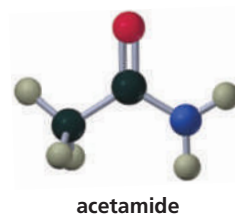
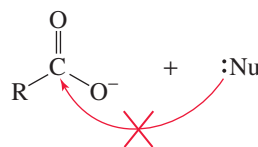
11.11 REACTIONS OF AMIDES

Amides are very unreactive compounds. They do not react with halide ions, alcohols, or water because, in each case, the incoming nucleophile is a weaker base than the leaving group of the amide (Table 11.1).

acetamide

$$\text{RCONHCH}_2CH_2CH_3 + Cl^- \longrightarrow \text{no reaction}$$

$$\text{RCONHCH}_3 + CH_3OH \longrightarrow \text{no reaction}$$

$$\text{RCONHCH}_2CH_3 + H_2O \longrightarrow \text{no reaction}$$

We will see, however, that amides do react with water and alcohols if an acid is present to catalyze the reaction (Section 11.12).

Dalmatians: Do Not Fool with Mother Nature

When amino acids are metabolized, the excess nitrogen is concentrated into uric acid, a compound with five amide bonds. A series of hydrolysis reactions, each catalyzed by a different enzyme, degrade uric acid—one amide bond at a time—all the way to ammonium ion. The extent to which uric acid is degraded depends on the species. Primates, birds, reptiles, and insects excrete excess nitrogen as uric acid. Other mammals excrete excess nitrogen as allantoin. Excess nitrogen in aquatic animals is excreted as allantoic acid, urea, or as ammonium salts.

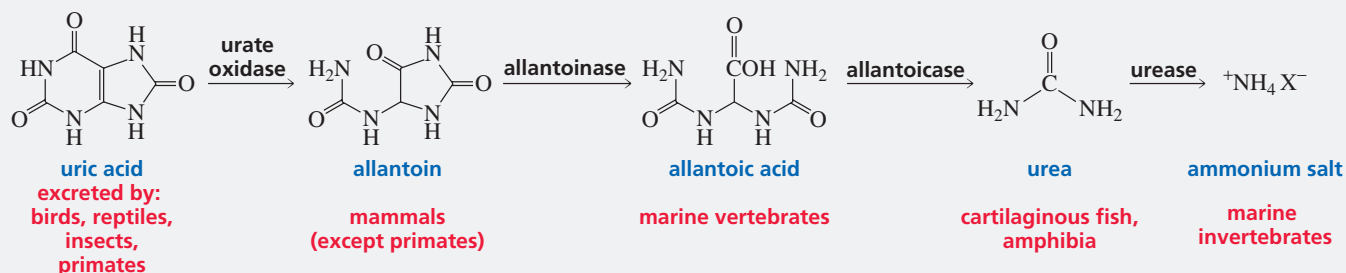
uric acid —urate oxidase→ allantoin —allantoinase→ allantoic acid —allantoicase→ urea —urease→ $^{+}NH_4\ X^-$ (ammonium salt)

uric acid excreted by: birds, reptiles, insects, primates

allantoin: mammals (except primates)

allantoic acid: marine vertebrates

urea: cartilaginous fish, amphibia

ammonium salt: marine invertebrates

Dalmatians, unlike other dogs, excrete high levels of uric acid. This is because breeders of Dalmatians have selected dogs that have no white hairs in their black spots, and the gene that causes the white hairs is linked to the gene that causes uric acid to be hydrolyzed to allantoin. Dalmatians, therefore, are susceptible to gout, a painful buildup of uric acid in joints.

PROBLEM 21♦

Which of the following reactions would lead to the formation of an amide?

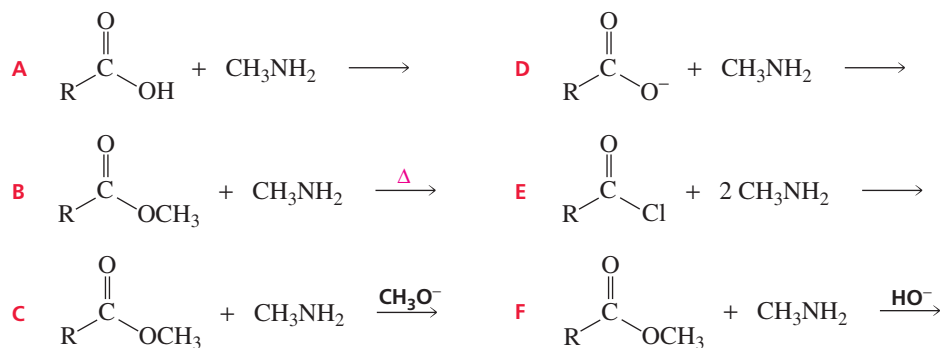
A $RCOOH + CH_3NH_2 \longrightarrow$

B $RCOOCH_3 + CH_3NH_2 \xrightarrow{\Delta}$

C $RCOOCH_3 + CH_3NH_2 \xrightarrow{CH_3O^-}$

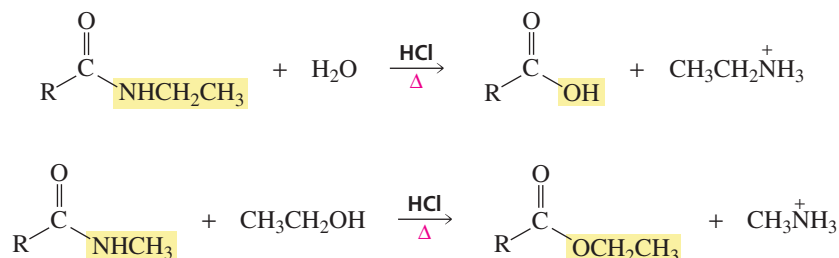
D $RCOO^- + CH_3NH_2 \longrightarrow$

E $RCOCl + 2\ CH_3NH_2 \longrightarrow$

F $RCOOCH_3 + CH_3NH_2 \xrightarrow{HO^-}$

11.12 ACID-CATALYZED AMIDE HYDROLYSIS AND ALCOHOLYSIS

Amides react with water to form carboxylic acids and with alcohols to form esters, if the reaction mixture is heated in the presence of an acid.

$$RCONHCH_2CH_3 + H_2O \xrightarrow[\Delta]{HCl} RCOOH + CH_3CH_2\overset{+}{N}H_3$$

$$RCONHCH_3 + CH_3CH_2OH \xrightarrow[\Delta]{HCl} RCOOCH_2CH_3 + CH_3\overset{+}{N}H_3$$

The mechanism for the acid-catalyzed hydrolysis of an amide is exactly the same as the mechanism for the acid-catalyzed hydrolysis of an ester shown on page 435.

MECHANISM FOR THE ACID-CATALYZED HYDROLYSIS OF AN AMIDE

the acid protonates the carbonyl oxygen

the nucleophile adds to the carbonyl carbon

tetrahedral intermediate I

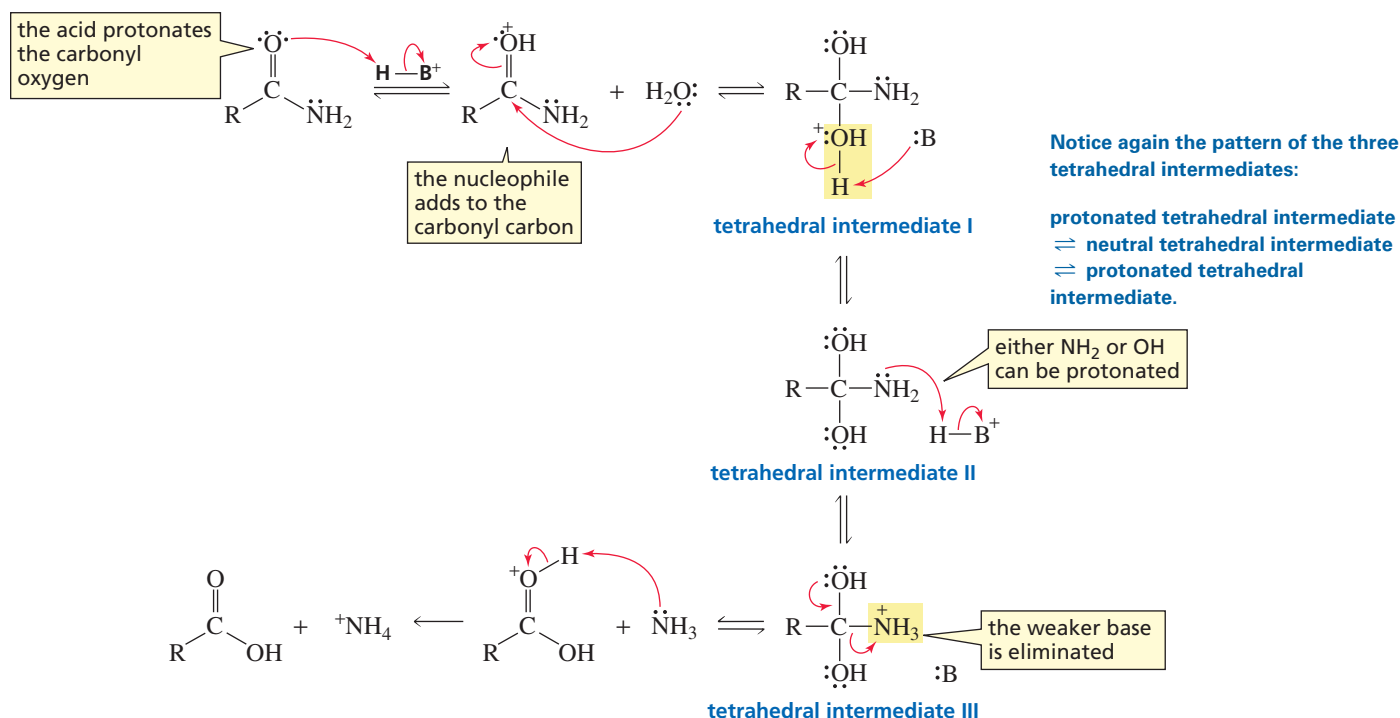
Notice again the pattern of the three tetrahedral intermediates:

protonated tetrahedral intermediate ⇌ neutral tetrahedral intermediate ⇌ protonated tetrahedral intermediate.

either NH_2 or OH can be protonated

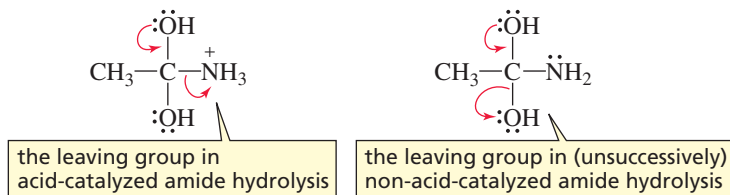
tetrahedral intermediate II

the weaker base is eliminated

tetrahedral intermediate III

- The acid protonates the carbonyl oxygen, which increases the susceptibility of the carbonyl carbon to nucleophilic addition.
- Addition of the nucleophile (H_2O) to the carbonyl carbon leads to tetrahedral intermediate I, which is in equilibrium with its nonprotonated form, tetrahedral intermediate II.
- Re-protonation can occur either on oxygen to re-form tetrahedral intermediate I or on nitrogen to form tetrahedral intermediate III. Protonation on nitrogen is favored because the NH_2 group is a stronger base than the OH group.
- Of the two possible leaving groups in tetrahedral intermediate III (HO^- and NH_3), NH_3 is the weaker base, so it is the one eliminated.
- Because the reaction is carried out in an acidic solution, NH_3 will be protonated after it is eliminated from the tetrahedral intermediate. This prevents the reverse reaction from occurring since $^+NH_4$ is not a nucleophile.

Let's take a minute to see why an amide cannot be hydrolyzed without a catalyst. In an uncatalyzed reaction, the amide would not be protonated. Therefore, water, a very poor nucleophile, would have to add to a neutral amide that is much less susceptible to nucleophilic addition than a protonated amide would be. More importantly, in the uncatalyzed reaction, the NH_2 group of the tetrahedral intermediate would not be protonated. Therefore, HO^- would be eliminated from the tetrahedral intermediate (because HO^- is a weaker base than $^-NH_2$), which would re-form the amide.

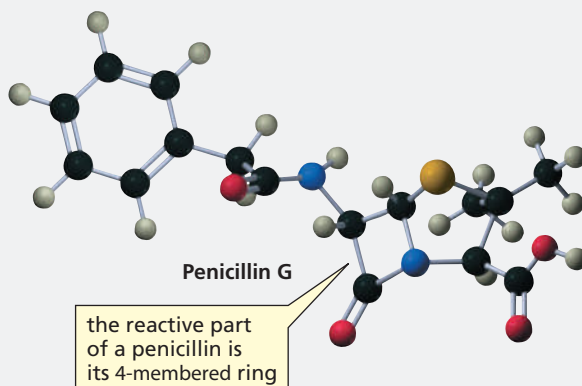
the leaving group in acid-catalyzed amide hydrolysis

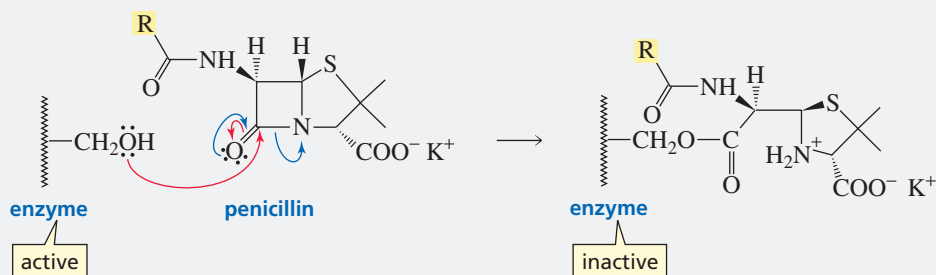
the leaving group in (unsuccessively) non-acid-catalyzed amide hydrolysis

When an amide reacts with an alcohol in the presence of acid to form an ester, it follows the same mechanism as it does when it reacts with water to form a carboxylic acid.

The Discovery of Penicillin

Sir Alexander Fleming was a professor of bacteriology at the University of London. The story is told that one day Fleming was about to throw away a culture of staphylococcal bacteria that had been contaminated by a rare strain of the mold *Penicillium notatum.* He noticed that the bacteria had disappeared wherever there was a particle of mold. This suggested to him that the mold must have produced an antibacterial substance. Ten years later, in 1938, the active substance—penicillin G—was isolated but the delay allowed the sulfa drugs to be the first antibiotics (Section 18.13).

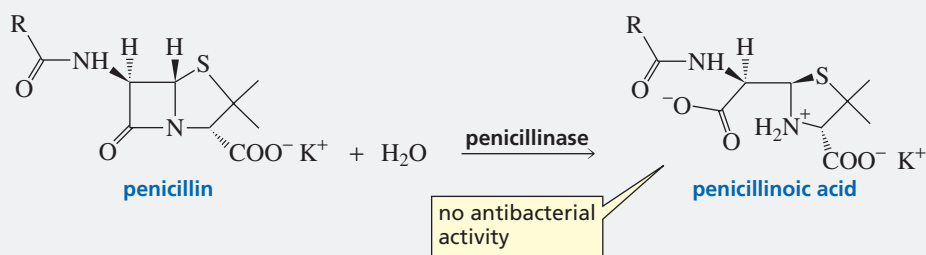
After penicillin G was found to cure bacterial infections in mice, it was used successfully in 1941 on nine cases of human bacterial infections. By 1943, it was being produced for the military and was first used for war casualties in Sicily and Tunisia. The drug became available to the civilian population in 1944. The pressure of the war made the determination of penicillin G's structure a priority because once its structure was determined, large quantities of the drug could conceivably be synthesized.

Penicillin and Drug Resistance

The antibiotic activity of penicillin results from its ability to acylate (put an acyl group on) a CH_2OH group of an enzyme that has a role in the synthesis of bacterial cell walls. Acylation occurs by a nucleophilic acyl substitution reaction: the CH_2OH group adds to the carbonyl carbon of the four-membered ring amide, forming a tetrahedral intermediate (red arrows). The four-membered ring amide is more reactive than a noncyclic amide because when the π bond re-forms, the strain in the four-membered ring is released when the amino group is eliminated (blue arrows).

enzyme — CH_2OH (active) + penicillin ($COO^-\ K^+$) ⟶ enzyme — CH_2O—C(=O)— ... H_2N^+ ... $COO^-\ K^+$ (inactive)

Acylation inactivates the enzyme, and actively growing bacteria die because they are unable to synthesize functional cell walls. Penicillin has no effect on mammalian cells because they are not enclosed by cell walls. Penicillins are stored at cold temperatures to minimize hydrolysis of the amide.

Bacteria that are resistant to penicillin secrete penicillinase, an enzyme that catalyzes hydrolysis of the amide. The ring-opened product has no antibacterial activity.

penicillin ($COO^-\ K^+$) + H_2O —penicillinase⟶ penicillinoic acid (^-O—C(=O)—, H_2N^+, $COO^-\ K^+$)

no antibacterial activity

Penicillins in Clinical Use

More than 10 different penicillins are currently in clinical use. They differ only in the group (R) attached to the carbonyl group. The variable groups (R) of these penicillins are shown here. In addition to their structural differences, the penicillins differ in the organisms against which they are most effective. They also differ in their susceptibility to penicillinase. For example, methicillin, a synthetic penicillin, is effective against bacteria that are resistant to penicillin G, a naturally occurring penicillin. Almost 19% of humans are allergic to penicillin G.

R

$C_6H_5CH_2-$ penicillin G

$C_6H_5CH(NH_2)-$ ampicillin

2,6-dimethoxyphenyl (OCH_3, OCH_3) methicillin

R

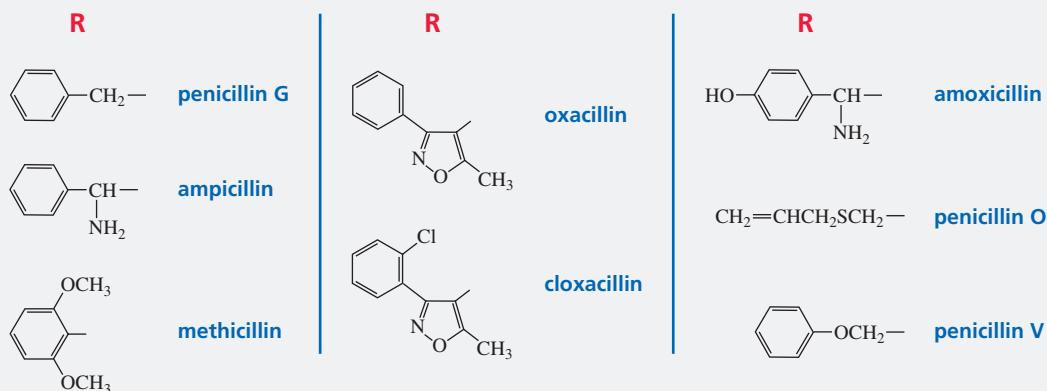
oxacillin (CH_3, N, O)

cloxacillin (Cl, CH_3, N, O)

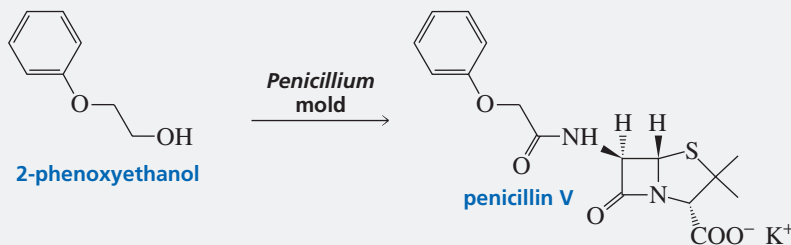
R

HO–C_6H_4–$CH(NH_2)-$ amoxicillin

$CH_2{=}CHCH_2SCH_2-$ penicillin O

$C_6H_5OCH_2-$ penicillin V

A Semisynthetic Penicillin

Penicillin V is a semisynthetic penicillin in clinical use. It is not a naturally occurring penicillin, but it is also not a true synthetic penicillin because chemists do not synthesize it. The *Penicillium* mold synthesizes it after being fed 2-phenoxyethanol, the compound needed for the R group.

2-phenoxyethanol $\xrightarrow{\textit{Penicillium}\ \text{mold}}$ penicillin V ($COO^-\ K^+$)

PROBLEM 22

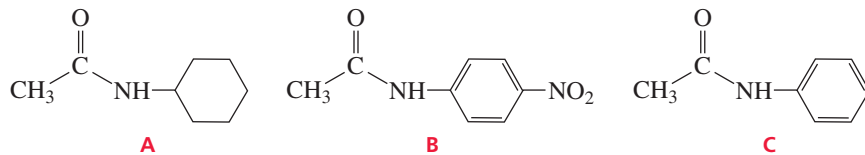
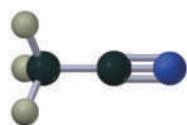
Write the mechanism for the acid-catalyzed reaction of an amide with an alcohol to form an ester.

PROBLEM 23♦

List the following amides in order from greatest reactivity to least reactivity toward acid-catalyzed hydrolysis:

A: $CH_3C(=O)NH$–cyclohexyl

B: $CH_3C(=O)NH$–C_6H_4–NO_2

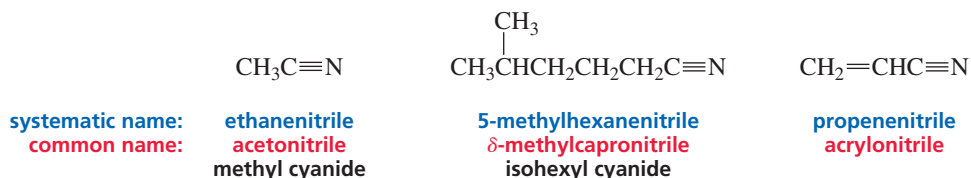
C: $CH_3C(=O)NH$–C_6H_5

11.13 NITRILES

acetonitrile

Nitriles are compounds that contain a cyano (C≡N) group. They are considered to be carboxylic acid derivatives because, like all the other carboxylic acid derivatives, they can be hydrolyzed to carboxylic acids.

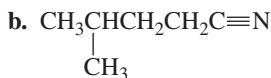
Naming Nitriles

In systematic nomenclature, nitriles are named by adding "nitrile" to the name of the parent alkane. Notice in the following examples that the triple-bonded carbon of the nitrile group is included in the number of carbons in the longest continuous chain.

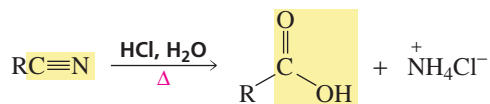
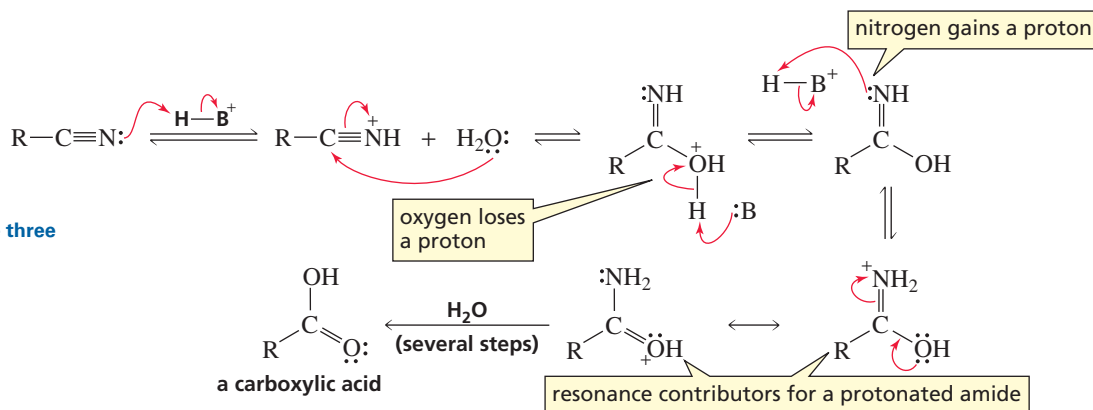
	$CH_3C\equiv N$	$CH_3CH(CH_3)CH_2CH_2CH_2C\equiv N$	$CH_2{=}CHC\equiv N$
systematic name:	ethanenitrile	5-methylhexanenitrile	propenenitrile
common name:	acetonitrile	δ-methylcapronitrile	acrylonitrile
	methyl cyanide	isohexyl cyanide	

In common nomenclature, nitriles are named by replacing "ic acid" of the carboxylic acid name with "onitrile." They can also be named as alkyl cyanides—using the name of the alkyl group that is attached to the triply bonded carbon.

PROBLEM 24♦

Give two names for each of the following nitriles:

a. $CH_3CH_2CH_2C\equiv N$ **b.** $CH_3CH(CH_3)CH_2CH_2C\equiv N$

Reactions of Nitriles

Nitriles are even harder to hydrolyze than amides, but they slowly hydrolyze to carboxylic acids when heated with water and an acid.

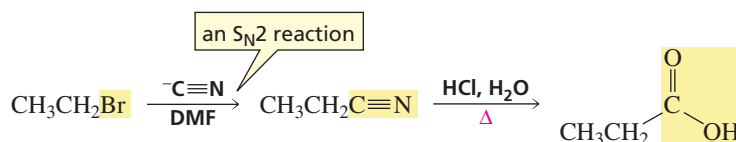
$$RC\equiv N \xrightarrow[\Delta]{HCl,\ H_2O} RC(=O)OH + \overset{+}{N}H_4Cl^-$$

MECHANISM FOR THE ACID-CATALYZED HYDROLYSIS OF A NITRILE

Notice again the pattern of the three intermediates:
protonated intermediate ⇌
neutral intermediate ⇌
protonated intermediate.

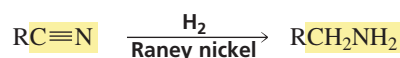
- The acid protonates the nitrogen of the cyano group, which makes the carbon of the cyano group more susceptible to the addition of water. (The addition of water to a protonated cyano group is analogous to the addition of water to a protonated carbonyl group.)

- A base removes a proton from oxygen, forming a neutral species that can be reprotonated on oxygen or protonated on nitrogen. Protonation on nitrogen forms a protonated amide, whose two resonance contributors are shown.
- The protonated amide is immediately hydrolyzed to a carboxylic acid—because an amide is easier to hydrolyze than a nitrile—by means of the acid-catalyzed mechanism shown on page 443.

Nitriles can be prepared from an S_N2 reaction of alkyl halide with cyanide ion. Because a nitrile can be hydrolyzed to a carboxylic acid, you now know how to convert an alkyl halide into a carboxylic acid. Notice that the carboxylic acid has one more carbon than the alkyl halide.

$$CH_3CH_2Br \xrightarrow[\text{DMF}]{^-C\equiv N} CH_3CH_2C\equiv N \xrightarrow[\Delta]{\text{HCl, } H_2O} CH_3CH_2COOH$$

an S_N2 reaction

Catalytic hydrogenation of a nitrile is another way to make a primary amine. Raney nickel is the preferred metal catalyst for this reduction.

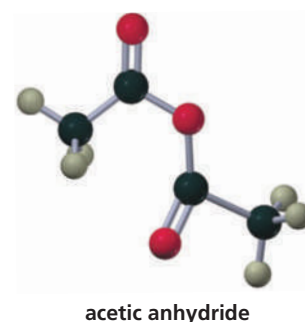
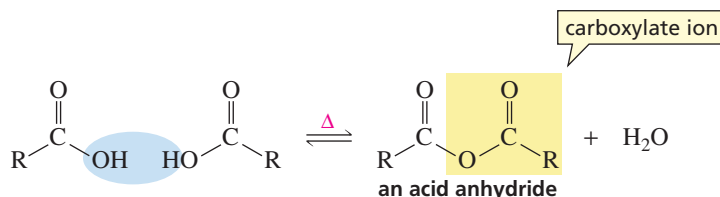
$$RC\equiv N \xrightarrow[\text{Raney nickel}]{H_2} RCH_2NH_2$$

PROBLEM 25♦

Which alkyl halides form the carboxylic acids listed here after reaction with sodium cyanide followed by heating the product in an acidic aqueous solution?

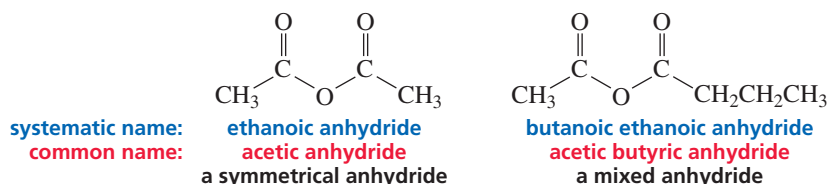
a. butyric acid **b.** isovaleric acid **c.** hexanoic acid

11.14 ACID ANHYDRIDES

Loss of water from two molecules of a carboxylic acid results in an **acid anhydride.** "Anhydride" means "without water." Therefore, an acid anhydride can be prepared by heating a carboxylic acid. An anhydride is a *carboxylic acid derivative*, because the OH of a carboxylic acid has been replaced by a carboxylate ion.

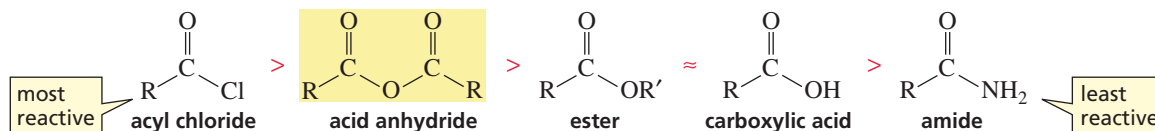
acetic anhydride

Naming Anhydrides

If the two carboxylic acid molecules forming the acid anhydride are the same, then the anhydride is a **symmetrical anhydride.** If they are different, then it is a **mixed anhydride.** Symmetrical anhydrides are named by replacing "acid" in the acid name with "anhydride." Mixed anhydrides are named by stating the names of both acids in alphabetical order, followed by "anhydride."

	$CH_3C(=O)OC(=O)CH_3$	$CH_3C(=O)OC(=O)CH_2CH_2CH_3$
systematic name:	ethanoic anhydride	butanoic ethanoic anhydride
common name:	acetic anhydride	acetic butyric anhydride
	a symmetrical anhydride	a mixed anhydride

Reactions of Anhydrides

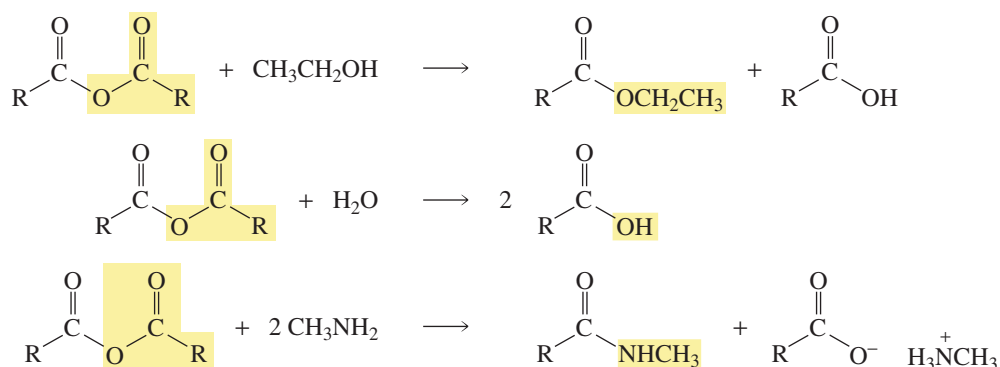
The leaving group of an anhydride is a carboxylate ion (its conjugate acid has a pK_a of ~5), which means that an anhydride is less reactive than an acyl chloride but more reactive than an ester or a carboxylic acid (Table 11.1).

relative reactivities of carboxylic acid derivatives

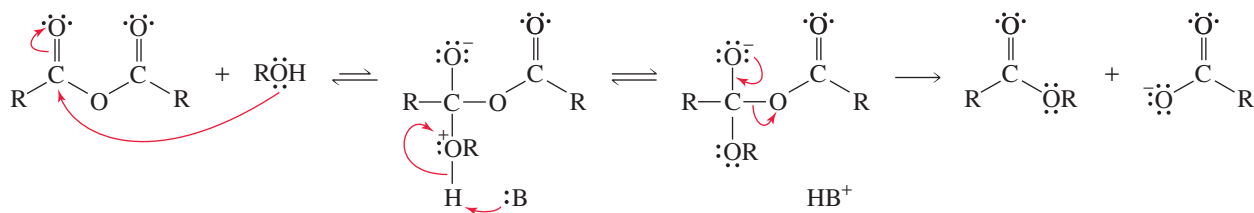
most reactive — acyl chloride (RCOCl) > acid anhydride (RCOOCOR) > ester (RCOOR′) ≈ carboxylic acid (RCOOH) > amide ($RCONH_2$) — least reactive

Therefore, an acid anhydride reacts with an alcohol to form an ester and a carboxylic acid, with water to form two equivalents of a carboxylic acid, and with an amine to form an amide and a carboxylate ion. In each case, the incoming nucleophile—after it loses a proton—is a stronger base than the departing carboxylate ion. (Recall that a carboxylic acid derivative can be converted to one that is less reactive but not to one that is more reactive; Section 11.12.)

$$RCOOCOR + CH_3CH_2OH \longrightarrow RCOOCH_2CH_3 + RCOOH$$

$$RCOOCOR + H_2O \longrightarrow 2\ RCOOH$$

$$RCOOCOR + 2\ CH_3NH_2 \longrightarrow RCONHCH_3 + RCOO^- \quad H_3\overset{+}{N}CH_3$$

In the reaction of an amine with an anhydride, two equivalents of amine must be used so that sufficient amine will be present to react with both the carbonyl compound and the proton produced in the reaction (Section 11.6).

The reactions of acid anhydrides follow the same mechanisms described in Section 11.6. For example, compare the mechanism for the reaction of an acid anhydride with an alcohol to the mechanism for the reaction of an acyl chloride with an alcohol on page 446.

MECHANISM FOR THE REACTION OF AN ACID ANHYDRIDE WITH AN ALCOHOL

$$RCOOCOR + R\ddot{O}H \rightleftharpoons \text{tetrahedral intermediate } (R-C(O^-)(\overset{+}{O}HR)-OCOR)\ :B \rightleftharpoons R-C(O^-)(OR)-OCOR\ \ HB^+ \longrightarrow RCOOR + {}^-OCOR$$

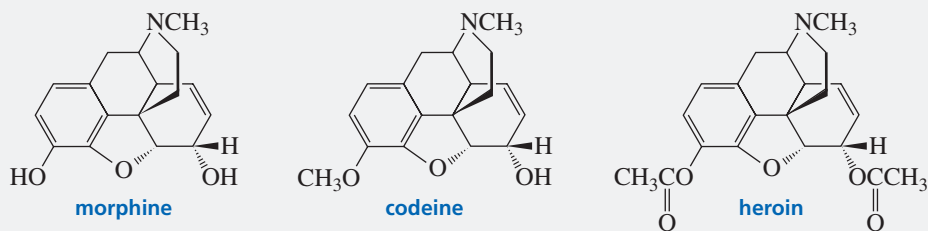
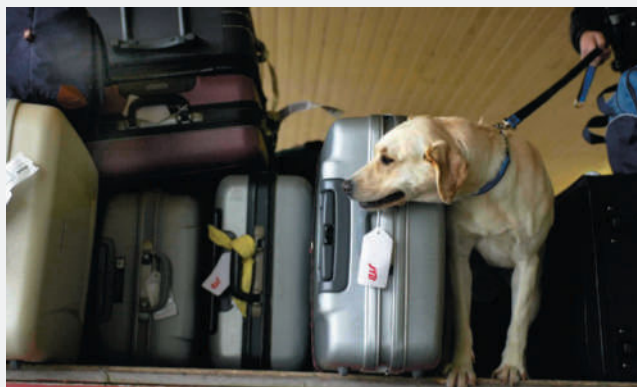
- The nucleophile adds to the carbonyl carbon, forming a tetrahedral intermediate.
- A proton is removed from the tetrahedral intermediate.
- The carboxylate ion, the weaker of the two bases in the tetrahedral intermediate, is eliminated.

What Drug-Enforcement Dogs Are Really Detecting

Morphine, the most widely used analgesic for severe pain, is the standard by which other painkilling medications are measured. Although scientists have learned how to synthesize morphine, most commercial morphine is obtained from opium, a milky fluid exuded by a species of poppy (see page 30). Morphine occurs in opium at concentrations as high as 10%. Opium was used for its analgesic properties as early as 4000 B.C. In Roman times, both opium use and opium addiction were widespread. Methylating one of the OH groups of morphine produces codeine, which has one-tenth the analgesic activity of morphine. Codeine profoundly inhibits the cough reflex.

NCH_3 … HO … O … H … OH — **morphine**

NCH_3 … CH_3O … O … H … OH — **codeine**

NCH_3 … $CH_3\overset{O}{\overset{\|}{C}}O$ … O … H … $O\overset{O}{\overset{\|}{C}}CH_3$ — **heroin**

Heroin, which is much more potent (and more widely abused) than morphine, is synthesized by treating morphine with acetic anhydride. This puts an acetyl group on each of the OH groups of morphine. Therefore, acetic acid is also formed as a product. To detect heroin, drug-enforcement agencies use dogs trained to recognize the pungent odor of acetic acid.

PROBLEM 26

a. Propose a mechanism for the reaction of acetic anhydride with water.
b. How does this mechanism differ from the mechanism for the reaction of acetic anhydride with an alcohol?

PROBLEM 27

Propose a mechanism for the reaction of an acyl chloride with acetate ion to form an acid anhydride.

PROBLEM 28♦

a. What acyl chloride and carboxylate ion could be used to form the mixed anhydride shown on page 447?
b. What other set of reagents could be used?

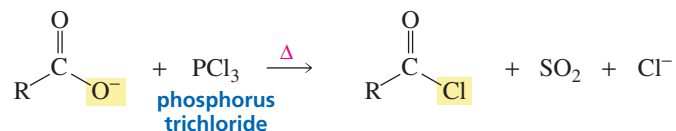
11.15 HOW CHEMISTS ACTIVATE CARBOXYLIC ACIDS

Of the various classes of carbonyl compounds discussed in this chapter—acyl chlorides, acid anhydrides, esters, carboxylic acids, and amides—carboxylic acids are the most commonly available, both in the laboratory and in cells. Therefore, carboxylic acids are

the reagents most likely to be available when a chemist or a cell needs to synthesize a carboxylic acid derivative. However, we have seen that carboxylic acids are relatively unreactive toward nucleophilic acyl substitution reactions because the OH group of a carboxylic acid is a strong base and, therefore, a poor leaving group. And at physiological pH (pH = 7.4), a carboxylic acid is even more resistant to nucleophilic acyl substitution reactions because it exists predominantly in its unreactive, negatively charged basic form. Therefore, both organic chemists and cells need a way to activate carboxylic acids so that they can readily undergo nucleophilic acyl substitution reactions. First we will look at how chemists activate carboxylic acids, and then we will see how cells do it.

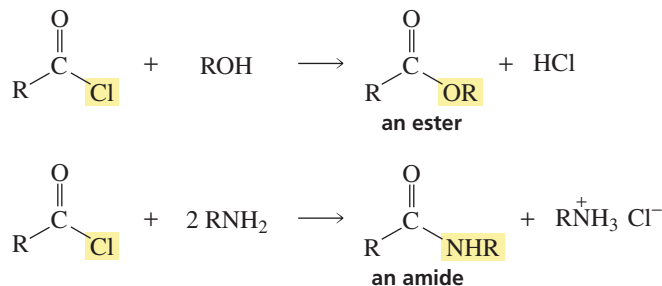
One way organic chemists activate carboxylic acids is by converting them into acyl chlorides, the most reactive of the carboxylic acid derivatives. A carboxylic acid can be converted into an acyl chloride by being heated with phosphorus trichloride (PCl_3).

$$RCOO^- + PCl_3 \xrightarrow{\Delta} RCOCl + SO_2 + Cl^-$$

phosphorus trichloride

Once the acyl chloride has been prepared, a wide variety of carboxylic acid derivatives can be synthesized by adding the appropriate nucleophile.

$$RCOCl + ROH \longrightarrow RCOOR + HCl$$

an ester

$$RCOCl + 2\,RNH_2 \longrightarrow RCONHR + R\overset{+}{N}H_3\ Cl^-$$

an amide

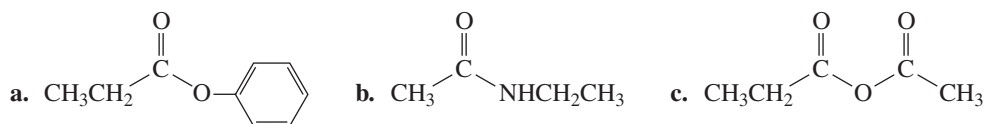
PROBLEM 29♦

What acyl chloride and what amine would be required to synthesize the following amides?

a. *N*-ethylbutanamide **b.** *N,N*-dimethylethanamide

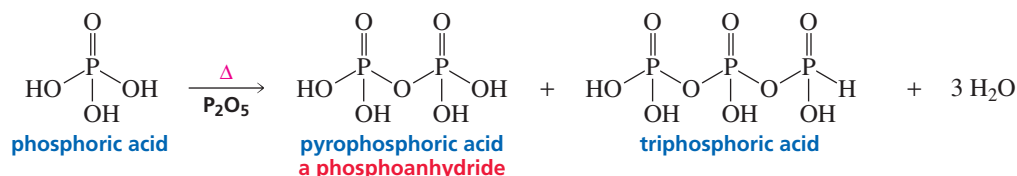
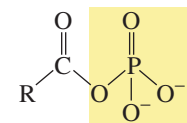
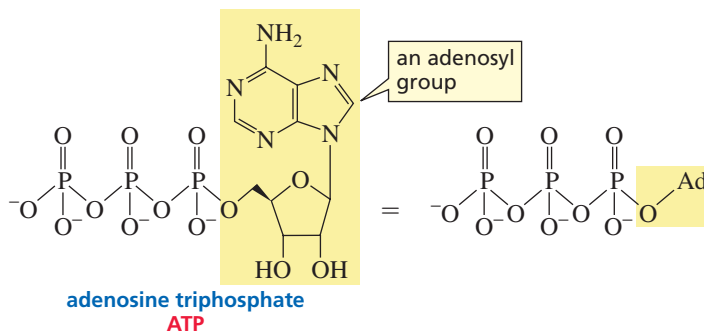
PROBLEM 30♦

How would you synthesize the following compounds starting with a carboxylic acid?

a. $CH_3CH_2COO\text{–}C_6H_5$ **b.** $CH_3CONHCH_2CH_3$ **c.** $CH_3CH_2COOCOCH_3$

11.16 HOW CELLS ACTIVATE CARBOXYLIC ACIDS

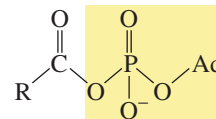
The synthesis of compounds by a living organism is called **biosynthesis.** Acyl chlorides and acid anhydrides are too reactive to be used as reagents in cells. Cells live in a predominantly aqueous environment, and acyl halides and acid anhydrides are rapidly hydrolyzed in water. So cells must activate carboxylic acids in a different way.

When phosphoric acid is heated with P_2O_5 (a dehydrating agent), it loses water, forming a phosphoanhydride called pyrophosphoric acid. Its name comes from *pyr,* the Greek word for "fire," since pyrophosphoric acid is prepared by "fire"—that is, by heating. Triphosphoric acid and higher polyphosphoric acids are also formed.

phosphoric acid → (Δ, P_2O_5) pyrophosphoric acid (a phosphoanhydride) + triphosphoric acid + $3\ H_2O$

One way cells can activate a carboxylic acid is to use adenosine triphosphate (ATP) to convert the carboxylic acid into an **acyl phosphate** or an **acyl adenylate**—carbonyl compounds with good leaving groups. ATP is an ester of triphosphoric acid. Its structure is shown here, both in its entirety and with "Ad" in place of the adenosyl group.

an acyl phosphate

an acyl adenylate

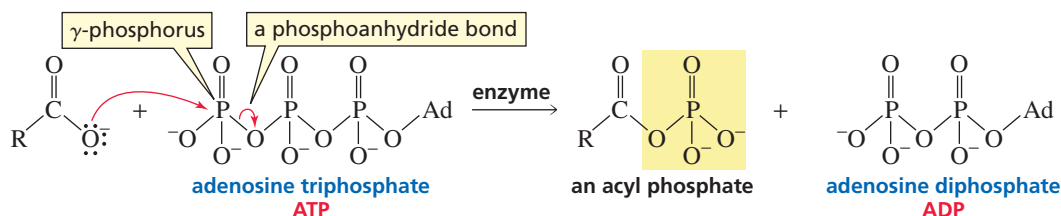
an adenosyl group

adenosine triphosphate
ATP

Acyl phosphates and acyl adenylates are mixed anhydrides of a carboxylic acid and phosphoric acid.

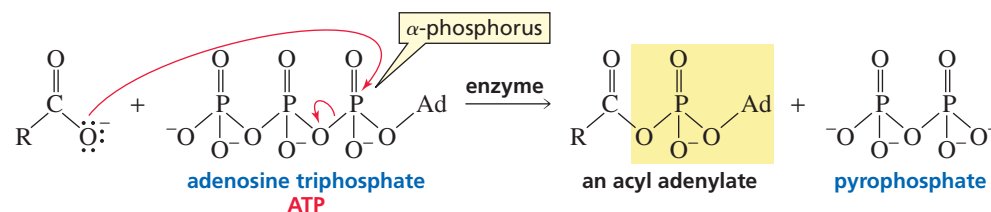
An acyl phosphate is formed by nucleophilic attack of a carboxylate ion on the γ-phosphorus (the phosphorus farthest away from the adenosyl group) of ATP. Attack of the nucleophile breaks the **phosphoanhydride bond** (rather than the π bond), so an intermediate is not formed. Essentially, it is an S_N2 reaction with an adenosine diphosphate (ADP) leaving group.

γ-phosphorus

a phosphoanhydride bond

adenosine triphosphate ATP —enzyme→ an acyl phosphate + adenosine diphosphate ADP

An acyl adenylate is formed by nucleophilic attack of a carboxylate ion on the α-phosphorus of ATP (the phosphorus closest to the adenosyl group).

α-phosphorus

adenosine triphosphate ATP —enzyme→ an acyl adenylate + pyrophosphate

Whether a nucleophile attacks the γ-phosphorus or the α-phosphorus depends on the enzyme that catalyzes the reaction.

Because both the carboxylate anion and ATP are negatively charged, they cannot react with each other unless they are at the active site of an enzyme. One of the functions of the enzymes that catalyze these reactions is to neutralize the negative charges of ATP so

it can react with a nucleophile (Figure 11.2). Enzyme-catalyzed reactions that have ATP as one of the reactants require Mg^{2+}, which helps reduce the negative charge on ATP at the active site.

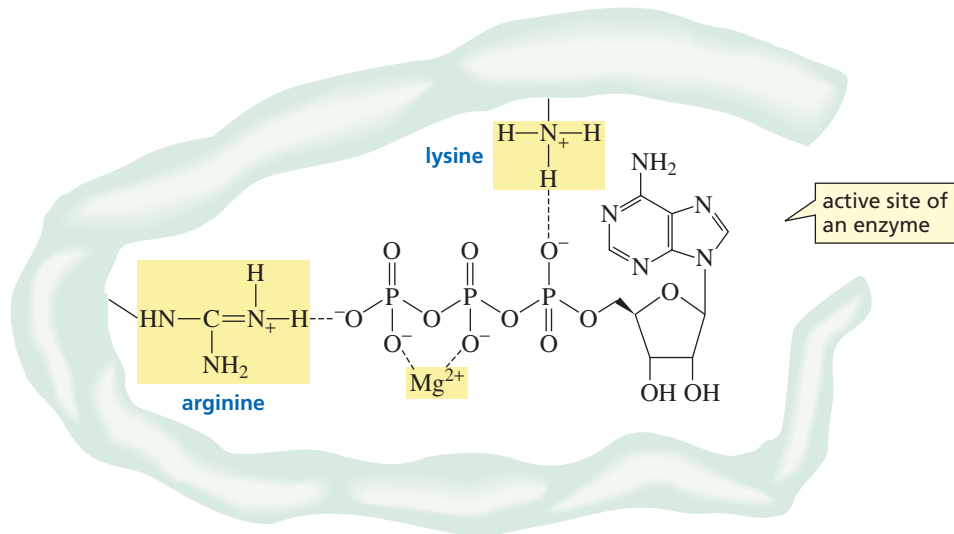
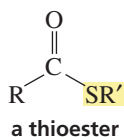



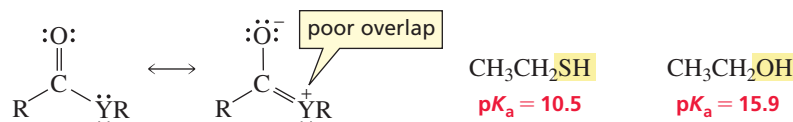
Figure 11.2
The interactions between ATP, Mg^{2+}, and positively charged groups at the active site of an enzyme.

a thioester

Cells can also activate a carboxylic acid by converting it to a thioester. A **thioester** is an ester with a sulfur in place of the alkoxy oxygen.

The carbonyl carbon of a thioester is more susceptible to nucleophilic addition than is the carbonyl carbon of an oxygen ester, because electron delocalization onto the carbonyl oxygen, which reduces the carbonyl group's reactivity, is weaker when Y is S than when Y is O (Section 11.6). Electron delocalization is weaker because less overlap occurs between the 3*p* orbital of sulfur and the 2*p* orbital of carbon than between the 2*p* orbital of oxygen and the 2*p* orbital of carbon.

poor overlap

CH_3CH_2SH pK_a = 10.5

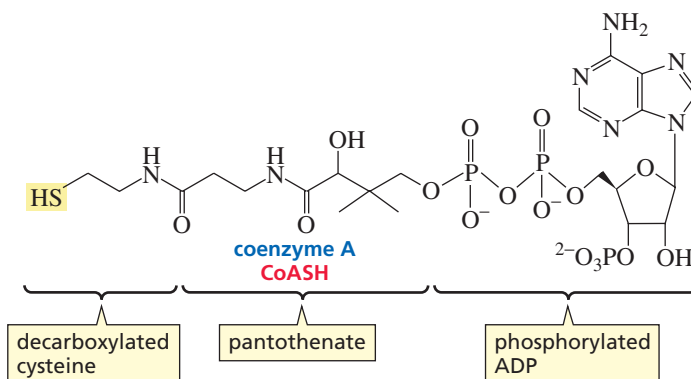
CH_3CH_2OH pK_a = 15.9

In addition, the tetrahedral intermediate formed from a thioester undergoes elimination more rapidly than the tetrahedral intermediate formed from an oxygen ester because a thiolate ion is a weaker base and is, therefore, easier to eliminate than an alkoxide ion.

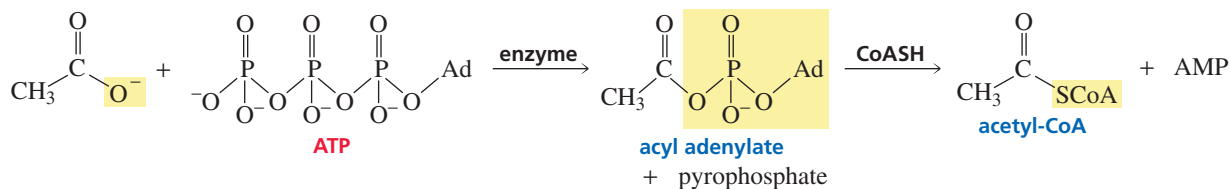
The thiol used in biological systems for the formation of thioesters is coenzyme A. The compound is written "CoASH" to emphasize that the thiol group is the reactive part of the molecule. CoASH is composed of a decarboxylated cysteine (an amino acid), pantothenate (a vitamin), and phosphorylated adenosine diphosphate.

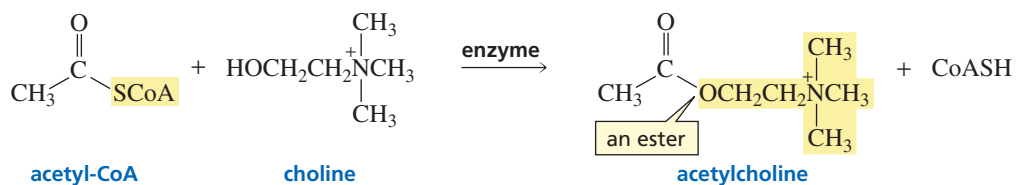
coenzyme A
CoASH

decarboxylated cysteine

pantothenate

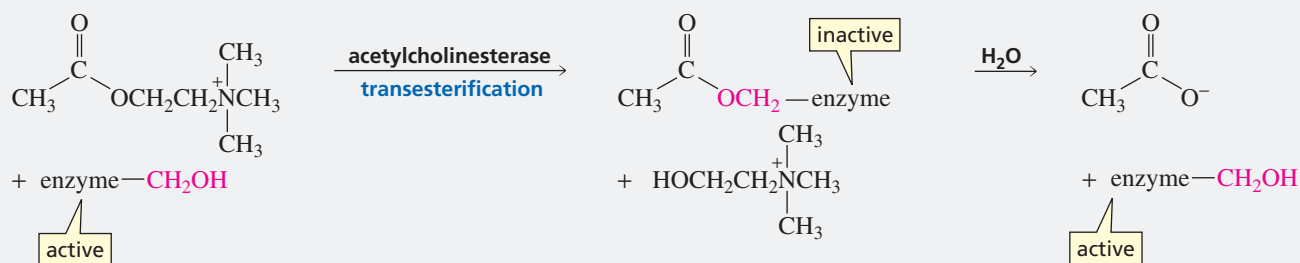
phosphorylated ADP

When a cell converts a carboxylic acid into a thioester, it first converts the carboxylic acid into an acyl adenylate. The acyl adenylate then reacts with CoASH to form the thioester. The most common thioester in cells is acetyl-CoA.

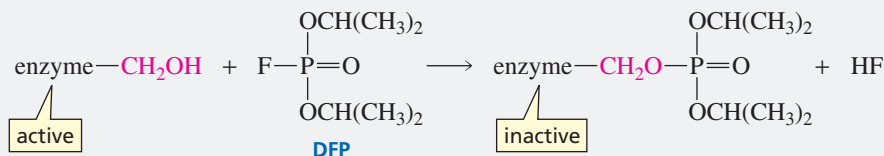
$$CH_3C(=O)O^- + \text{ATP} \xrightarrow{\text{enzyme}} CH_3C(=O)O{-}P(=O)(O^-){-}O{-}Ad \ (\text{acyl adenylate}) + \text{pyrophosphate} \xrightarrow{\text{CoASH}} CH_3C(=O)SCoA \ (\text{acetyl-CoA}) + \text{AMP}$$

Acetylcholine (an ester) is an example of a compound that cells synthesize using acetyl-CoA. Acetylcholine is a *neurotransmitter*—that is, it transmits nerve impulses across the synapses (spaces) between nerve cells.

$$CH_3C(=O)SCoA \ (\text{acetyl-CoA}) + HOCH_2CH_2\overset{+}{N}(CH_3)_3 \ (\text{choline}) \xrightarrow{\text{enzyme}} CH_3C(=O)OCH_2CH_2\overset{+}{N}(CH_3)_3 \ (\text{acetylcholine}) + \text{CoASH}$$

an ester

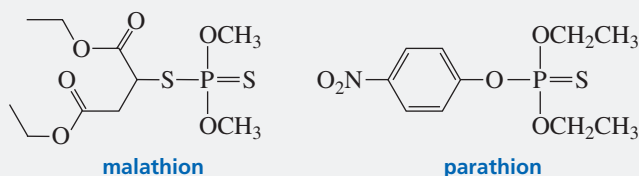
Nerve Impulses, Paralysis, and Insecticides

After an impulse is transmitted between two nerve cells, acetylcholine must be hydrolyzed immediately to enable the recipient cell to receive another impulse. Acetylcholinesterase, the enzyme that catalyzes this hydrolysis, has a CH_2OH group that is necessary for its catalytic activity. The CH_2OH group participates in a transesterification reaction with acetylcholine, which releases choline. Hydrolysis of the ester group attached to the enzyme restores its active form.

$$CH_3C(=O)OCH_2CH_2\overset{+}{N}(CH_3)_3 + \text{enzyme}{-}CH_2OH \ (\text{active}) \xrightarrow[\text{transesterification}]{\text{acetylcholinesterase}} CH_3C(=O)OCH_2{-}\text{enzyme} \ (\text{inactive}) + HOCH_2CH_2\overset{+}{N}(CH_3)_3 \xrightarrow{H_2O} CH_3C(=O)O^- + \text{enzyme}{-}CH_2OH \ (\text{active})$$

Diisopropyl fluorophosphate (DFP), a military nerve gas used during World War II, inactivates acetylcholinesterase by reacting with its CH_2OH group. When the enzyme is inactivated, nerve impulses cannot be transmitted properly and paralysis occurs. DFP is extremely toxic. Its LD_{50} (the lethal dose for 50% of the test animals) is only 0.5 mg/kg of body weight.

$$\text{enzyme}{-}CH_2OH \ (\text{active}) + F{-}P(=O)(OCH(CH_3)_2)_2 \ (\text{DFP}) \longrightarrow \text{enzyme}{-}CH_2O{-}P(=O)(OCH(CH_3)_2)_2 \ (\text{inactive}) + HF$$

Malathion and parathion, widely used as insecticides, are compounds related to DFP. The LD_{50} of malathion is 2800 mg/kg. Parathion is much more toxic, with an LD_{50} of 2 mg/kg.

malathion: $(CH_3O)_2P(=S){-}S{-}CH(CO_2CH_2CH_3)CH_2CO_2CH_2CH_3$

parathion: $O_2N{-}C_6H_4{-}O{-}P(=S)(OCH_2CH_3)_2$

SOME IMPORTANT THINGS TO REMEMBER

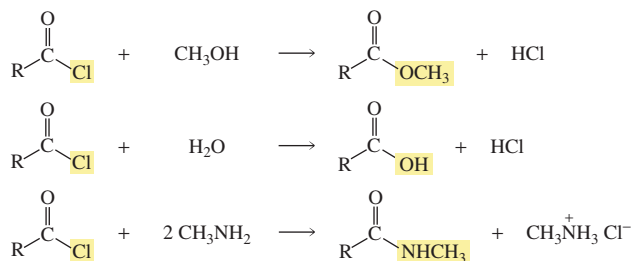
- A **carbonyl group** is a carbon double bonded to an oxygen; an **acyl group** is a carbonyl group attached to an alkyl (R) group.
- **Acyl chlorides, acid anhydrides, esters,** and **amides** are called **carboxylic acid derivatives** because they differ from a carboxylic acid only in the nature of the group that has replaced the OH group of the carboxylic acid.
- The reactivity of carbonyl compounds resides in the polarity of the carbonyl group; the carbonyl carbon has a partial positive charge that is attractive to nucleophiles.
- Carboxylic acids and carboxylic acid derivatives undergo **nucleophilic acyl substitution reactions,** reactions in which a nucleophile replaces the substituent attached to the acyl group in the reactant.
- A carboxylic acid or carboxylic acid derivative will undergo a nucleophilic acyl substitution reaction provided that the newly added group in the tetrahedral intermediate is a stronger base than the group attached to the acyl group in the reactant.
- Generally, a compound with an sp^3 carbon bonded to an oxygen is unstable if the sp^3 carbon is bonded to another electronegative atom.
- The weaker the base attached to the acyl group, the more easily both steps of the nucleophilic acyl substitution reaction can take place.
- The relative reactivities toward nucleophilic acyl substitution are acyl chlorides > acid anhydrides > esters ~ carboxylic acids > amides > carboxylate ions.
- **Hydrolysis, alcoholysis,** and **aminolysis** are reactions in which water, alcohols, and amines, respectively, convert one compound into two compounds.
- A **transesterification reaction** converts one ester to another ester.
- The rate of hydrolysis can be increased by acid or by HO^-; the rate of transesterifiction can be increased by acid or by RO^-.
- An acid increases the rate of formation of the tetrahedral intermediate by protonating the carbonyl oxygen, which increases the electrophilicity of the carbonyl carbon.
- An acid decreases the basicity of the leaving group by protonating it, which makes it easier to eliminate.
- Hydroxide (or alkoxide) ion increases the rate of formation of the tetrahedral intermediate—it is a better nucleophile than water (or an alcohol)—and increases the rate of collapse of the tetrahedral intermediate by creating a more stable transition state.
- Hydroxide ion promotes only hydrolysis reactions; alkoxide ion promotes only alcoholysis reactions.
- In an acid-catalyzed reaction, all organic reactants, intermediates, and products are positively charged or neutral; in hydroxide-ion- or alkoxide-ion-promoted reactions, all organic reactants, intermediates, and products are negatively charged or neutral.
- Amides are unreactive compounds but do react with water and alcohols if the reaction mixture is heated in an acidic solution.
- Nitriles are harder to hydrolyze than amides.
- Organic chemists activate carboxylic acids by converting them into acyl chlorides.
- Cells activate carboxylic acids by converting them into **acyl phosphates, acyl adenylates,** or **thioesters.**

SUMMARY OF REACTIONS

1. Reactions of acyl chlorides (Section 11.6). The mechanisms are shown on pages 445–446.

$$RC(=O)Cl + CH_3OH \longrightarrow RC(=O)OCH_3 + HCl$$

$$RC(=O)Cl + H_2O \longrightarrow RC(=O)OH + HCl$$

$$RC(=O)Cl + 2\,CH_3NH_2 \longrightarrow RC(=O)NHCH_3 + CH_3\overset{+}{N}H_3\,Cl^-$$

2. Reactions of esters (Sections 11.7–11.9). The mechanisms are shown on pages 449 and 451.

$$RCOOR + CH_3OH \xrightleftharpoons{HCl} RCOOCH_3 + ROH$$

$$RCOOR + CH_3OH \xrightarrow{CH_3O^-} RCOOCH_3 + ROH$$

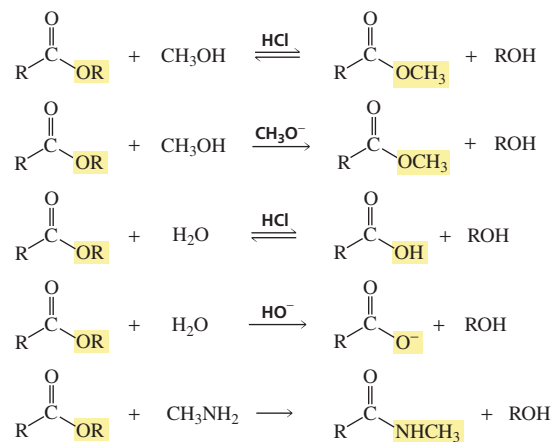
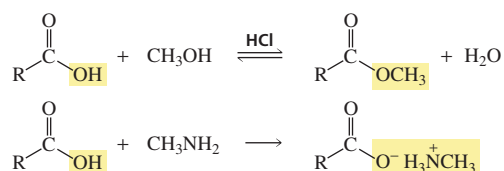
$$RCOOR + H_2O \xrightleftharpoons{HCl} RCOOH + ROH$$

$$RCOOR + H_2O \xrightarrow{HO^-} RCOO^- + ROH$$

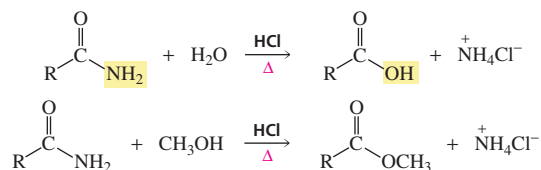
$$RCOOR + CH_3NH_2 \longrightarrow RCONHCH_3 + ROH$$

3. Reactions of carboxylic acids (Section 11.10).

$$RCOOH + CH_3OH \xrightleftharpoons{HCl} RCOOCH_3 + H_2O$$

$$RCOOH + CH_3NH_2 \longrightarrow RCOO^-\ H_3\overset{+}{N}CH_3$$

4. Reactions of amides (Sections 11.11–11.12). The mechanism is shown on page 457.

$$RCONH_2 + H_2O \xrightarrow[\Delta]{HCl} RCOOH + \overset{+}{N}H_4Cl^-$$

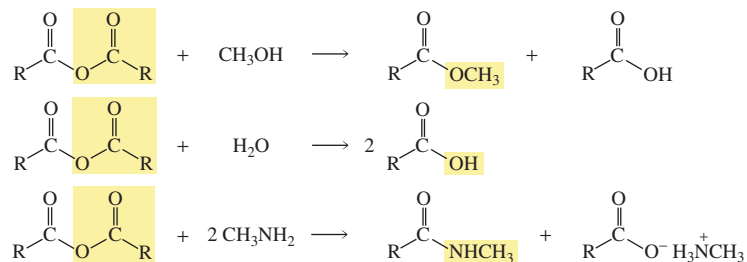
$$RCONH_2 + CH_3OH \xrightarrow[\Delta]{HCl} RCOOCH_3 + \overset{+}{N}H_4Cl^-$$

5. Hydrolysis of nitriles (Section 11.13). The mechanism is shown on page 460.

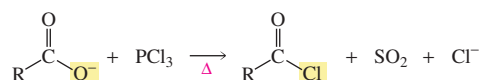
$$RC{\equiv}N + H_2O \xrightarrow[\Delta]{HCl} RCOOH + \overset{+}{N}H_4Cl^-$$

6. Reactions of acid anhydrides (Section 11.14). The mechanism is shown on page 463.

$$RCOOCOR + CH_3OH \longrightarrow RCOOCH_3 + RCOOH$$

$$RCOOCOR + H_2O \longrightarrow 2\ RCOOH$$

$$RCOOCOR + 2\ CH_3NH_2 \longrightarrow RCONHCH_3 + RCOO^-\ H_3\overset{+}{N}CH_3$$

7. Activation of carboxylic acids by chemists (Section 11.15).

$$RCOO^- + PCl_3 \xrightarrow{\Delta} RCOCl + SO_2 + Cl^-$$

8. Activation of carboxylic acids by cells (Section 11.16). The mechanisms are shown on pages 465 and 467.

acyl phosphate

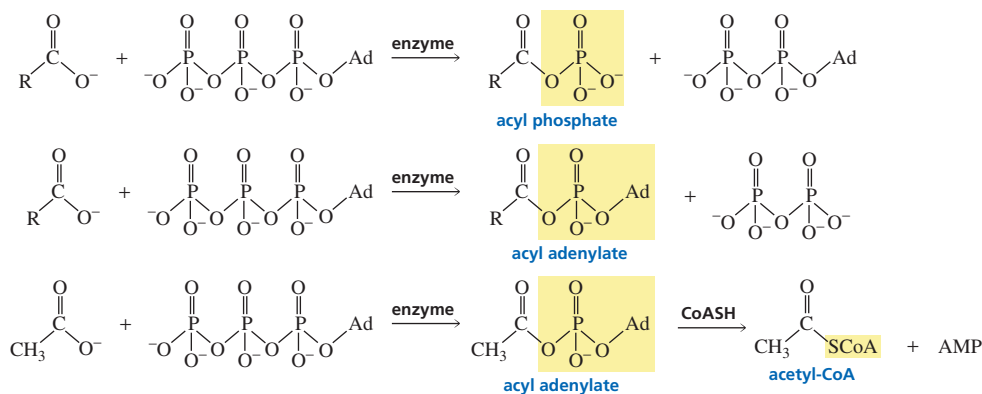
acyl adenylate

acyl adenylate

acetyl-CoA

enzyme

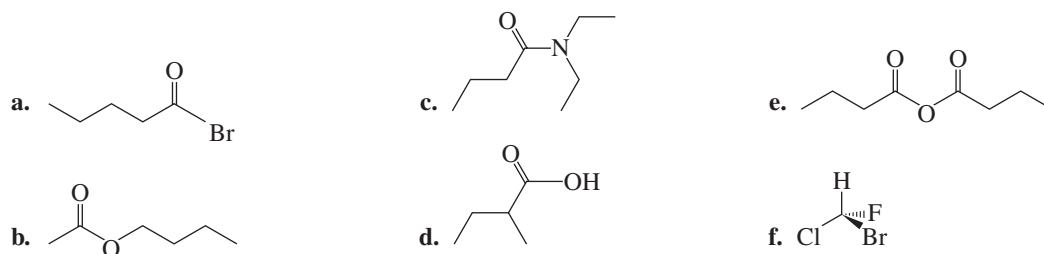
CoASH

+ AMP

PROBLEMS

31. Write a structure for each of the following:

a. *N*,*N*-diethylheptanamide
b. 2,2-dimethyloctanamide
c. butylamide
d. potassium formate
e. propionic anhydride
f. 2-methylpropanenitrile

32. Name the following compounds:

a. **b.** **c.** **d.** **e.** **f.**

33. Which ester is more reactive, methyl formate or methyl acetate?

34. What products would be formed from the reaction of acetyl chloride with the following reagents?

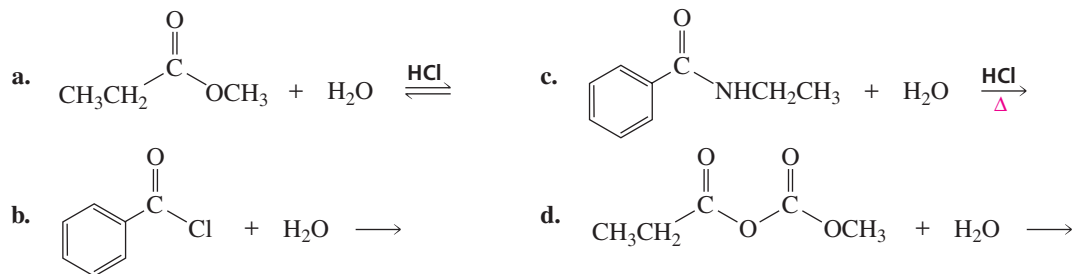
a. sodium acetate
b. excess dimethylamine
c. aqueous HCl
d. aqueous NaOH
e. cyclohexanol
f. isopropyl alcohol

35. What products would be obtained from the following hydrolysis reactions?

a. $CH_3CH_2C(=O)OCH_3 + H_2O \xrightleftharpoons{HCl}$

b. $C_6H_5C(=O)Cl + H_2O \longrightarrow$

c. $C_6H_5C(=O)NHCH_2CH_3 + H_2O \xrightarrow[\Delta]{HCl}$

d. $CH_3CH_2C(=O)OC(=O)OCH_3 + H_2O \longrightarrow$

36. If propionyl chloride is added to one equivalent of methylamine, only a 50% yield of *N*-methylpropanamide is obtained. If, however, the acyl chloride is added to two equivalents of methylamine, the yield of *N*-methylpropanamide is almost 100%. Explain these observations.

37. a. Which compound would you expect to have a higher dipole moment, methyl acetate or butanone?
b. Which would you expect to have a higher boiling point?

methyl acetate　　butanone

38. **a.** List the following esters in order of decreasing reactivity in the first slow step of a nucleophilic acyl substitution reaction (formation of the tetrahedral intermediate).

b. List the same esters in order of decreasing reactivity in the second slow step of a nucleophilic acyl substitution reaction (collapse of the tetrahedral intermediate).

A B C

39. D. N. Kursanov, a Russian chemist, proved that the bond that is broken in the hydroxide-ion-promoted hydrolysis of an ester is the acyl C—O bond, rather than the alkyl C—O bond, by studying the hydrolysis of the following ester under basic conditions:

alkyl C—O bond
acyl C—O bond

a. What product contained the ^{18}O label?
b. What product would have contained the ^{18}O label if the alkyl C—O bond had broken?

40. Write the equation for
a. the hydrolysis of propanoyl chloride.
b. the transesterification of ethyl butanoate with propanol.
c. the aminolysis of ethyl pentanoate.

41. Using an alcohol for one method and an alkyl halide for the other, show two ways to make each of the following esters:
a. propyl acetate (odor of pears)
b. isopentyl acetate (odor of bananas)
c. ethyl butyrate (odor of pineapple)
d. methyl phenylethanoate (odor of honey)

42. What reagents would you use to convert propyl ethanoate into the following compounds?
a. isopropyl ethanoate
b. sodium ethanoate
c. *N*-ethylethanamide
d. ethanoic acid

43. Which of the reaction coordinate diagrams represents the reaction of an ester with chloride ion?

b.
Free energy
Progress of the reaction

44. Aspartame, the sweetener used in the commercial products NutraSweet and Equal, is 200 times sweeter than sucrose. What products would be obtained if aspartame were hydrolyzed completely in an aqueous solution of HCl?

aspartame

45. An aqueous solution of a primary or secondary amine reacts with an acyl chloride to form an amide as the major product. However, if the amine is tertiary, an amide is not formed. What product *is* formed? Explain.

46. Is the base-catalyzed hydrolysis of ethyl ethanoate a reversible or an irreversible reaction? Explain.

47. When a student treated butanedioic acid with phosphorus trichloride, she was surprised to find that the product she obtained was an anhydride rather than an acyl chloride. Propose a mechanism to explain why she obtained an anhydride.

48. a. Which of the following reactions will not give the carbonyl product shown?
b. Which of the reactions that do not occur can be made to occur if an acid catalyst is added to the reaction mixture?

1. OH + O⁻ ⟶ anhydride
2. Cl + O⁻ ⟶ anhydride
3. NH_2 + Cl^- ⟶ Cl
4. OH + CH_3NH_2 ⟶ $NHCH_3$
5. OCH_3 + CH_3NH_2 $\xrightarrow{\Delta}$ $NHCH_3$
6. OCH_3 + Cl^- ⟶ Cl
7. $NHCH_3$ + O⁻ ⟶ anhydride
8. Cl + H_2O ⟶ OH
9. $NHCH_3$ + H_2O ⟶ OH
10. anhydride + CH_3OH ⟶ OCH_3

49. What are the products of the following reactions?

a. CH_3COCl + 2 NH_3 ⟶

b. lactam (NH) + H_2O $\xrightarrow[\Delta]{HCl}$

c. lactone + H_2O (excess) $\xrightarrow{HCl}$

d. cyclic anhydride + H_2O ⟶

e. benzoic acid (C₆H₅COOH) $\xrightarrow[2.\ 2\ CH_3NH_2]{1.\ PCl_3}$

f. cyclic anhydride + CH_3OH (excess) $\xrightarrow{HCl}$

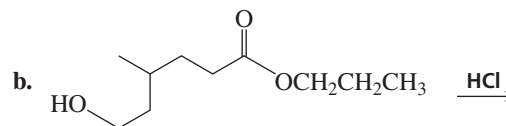
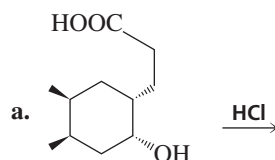
50. Show how the following compounds could be prepared from the given starting materials. You can use any necessary organic or inorganic reagents.

a. $CH_3CH_2C(=O)NH_2$ ⟶ $CH_3CH_2C(=O)Cl$

b. alcohol (OH) ⟶ carboxylic acid (C(=O)OH)

51. What product would you expect to obtain from each of the following reactions?

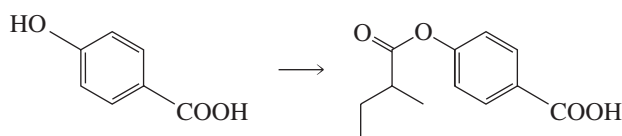
a. HOOC … OH $\xrightarrow{HCl}$

b. HO … C(=O)$OCH_2CH_2CH_3$ $\xrightarrow{HCl}$

52. a. When a carboxylic acid is dissolved in isotopically labeled water ($H_2{}^{18}O$) and an acid catalyst is added, the label is incorporated into both oxygens of the acid. Propose a mechanism to account for this.

$$CH_3C(=O)OH + H_2{}^{18}O \overset{HCl}{\rightleftharpoons} CH_3C(={}^{18}O){}^{18}OH + H_2O$$

b. If a carboxylic acid is dissolved in isotopically labeled methanol ($CH_3{}^{18}OH$) and an acid catalyst is added, where will the label reside in the product?

53. What reagent should be used to carry out the following reaction?

HO–C₆H₄–COOH ⟶ ester–C₆H₄–COOH

12 Reactions of Aldehydes and Ketones • More Reactions of Carboxylic Acid Derivatives

a yew tree forest

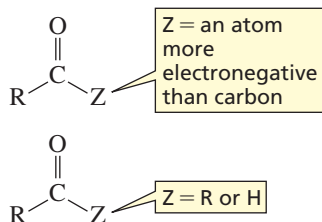
Taxol, a compound extracted from the bark of yew trees, was found to be an effective drug against several kinds of cancer. However, removing the bark kills the tree, the trees grow very slowly, and the bark of one tree provides only a small amount of the drug. Yew tree forests, moreover, are the home of the spotted owl—an endangered species. When chemists determined the structure of the drug, they were disappointed to find that it would be a very difficult compound to synthesize. Nevertheless, the current supply of taxol is sufficient to meet medical demands. In this chapter, you will see how this was accomplished.

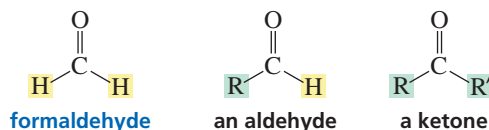
Group IV

O
‖
C
R Z

Z = an atom more electronegative than carbon

O
‖
C
R Z

Z = R or H

This chapter continues the discussion of the families of compounds in Group IV. Here we will look at the reactions of aldehydes and ketones—that is, carbonyl compounds that do not have a group that can be substituted by another group, and we will compare their reactions with those of the carboxylic acid derivatives that you studied in Chapter 11.

The carbonyl carbon of the simplest aldehyde, formaldehyde, is bonded to two hydrogens. The carbonyl carbon of all other **aldehydes** is bonded to a hydrogen and to an alkyl group (R). The carbonyl carbon of a **ketone** is bonded to two R groups.

Many compounds found in nature have aldehyde or ketone functional groups. Aldehydes have pungent odors, whereas ketones tend to smell sweet. Vanillin and cinnamaldehyde are examples of naturally occurring aldehydes. A whiff of vanilla extract will allow you to appreciate the pungent odor of vanillin. The ketones camphor and carvone

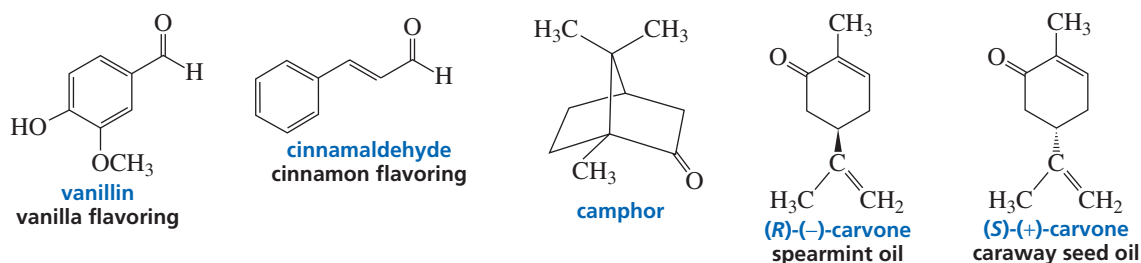
are responsible for the characteristic sweet odors of the leaves of camphor trees, spearmint leaves, and caraway seeds.

vanillin
vanilla flavoring

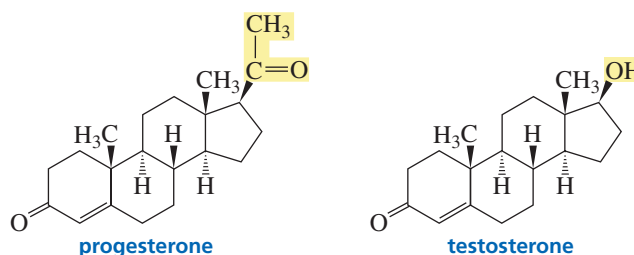
cinnamaldehyde
cinnamon flavoring

camphor

(*R*)-(−)-carvone
spearmint oil

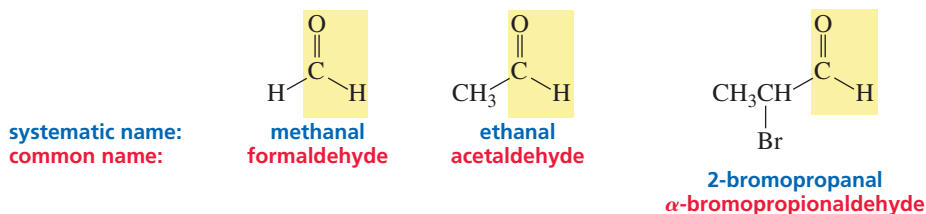
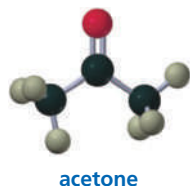
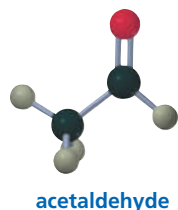
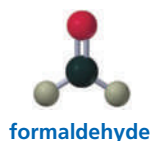
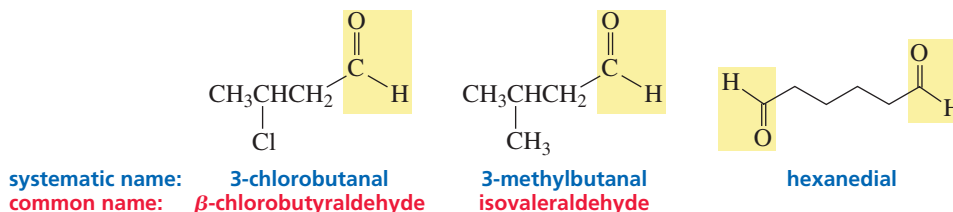
(*S*)-(+)-carvone
caraway seed oil

Progesterone and testosterone are two biologically important ketones that illustrate how a small difference in structure can be responsible for a large difference in biological activity. Both are sex hormones, but progesterone is synthesized primarily in the ovaries, whereas testosterone is synthesized primarily in the testes.

progesterone

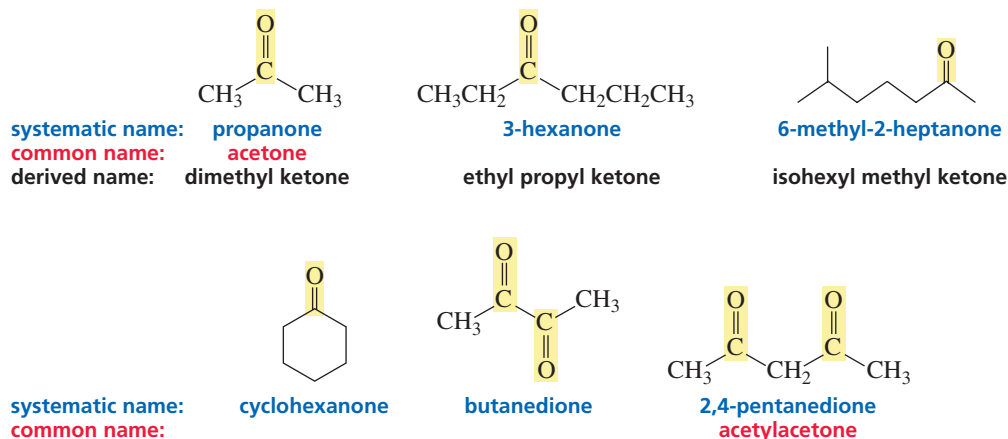
testosterone

12.1 THE NOMENCLATURE OF ALDEHYDES AND KETONES

Naming Aldehydes

The systematic (IUPAC) name of an aldehyde is obtained by replacing the final "e" on the name of the parent hydrocarbon with "al." For example, a one-carbon aldehyde is called methan*al*, and a two-carbon aldehyde is called ethan*al*. The position of the carbonyl carbon does not have to be designated because it is always at the end of the parent hydrocarbon (or else the compound would not be an aldehyde), so it always has the 1-position.

	HCHO	CH_3CHO	$CH_3CH(Br)CHO$
systematic name:	methanal	ethanal	2-bromopropanal
common name:	formaldehyde	acetaldehyde	α-bromopropionaldehyde

The common name of an aldehyde is the same as the common name of the corresponding carboxylic acid, except that "aldehyde" is substituted for "oic acid" (or "ic acid"). Recall that the position of a substituent is designated by a lowercase Greek letter when common names are used. The carbonyl carbon is not given a designation, so the carbon adjacent to the carbonyl carbon is the α-carbon (Section 11.1).

Notice that the terminal "e" of the parent hydrocarbon is not removed in hexanedial. (The "e" is removed only to avoid two successive vowels.)

Naming Ketones

The systematic name of a ketone is obtained by replacing the "e" on the end of the parent hydrocarbon name with "one." The chain is numbered in the direction that gives the carbonyl carbon the smaller number. Cyclic ketones do not need a number because the carbonyl carbon is assumed to be at the 1-position. Derived names can also be used for ketones. In a derived name, the substituents attached to the carbonyl group are cited in alphabetical order, followed by "ketone."

Aldehydes and ketones are named using a functional group suffix.

Only a few ketones have common names. The smallest ketone, propanone, is usually referred to by its common name, acetone. Acetone is a widely used laboratory solvent.

Butanedione: An Unpleasant Compound

Fresh perspiration is odorless. The smells we associate with perspiration result from a chain of events initiated by bacteria that are always present on our skin. These bacteria produce lactic acid, which creates an acidic environment that allows other bacteria to break down the components of perspiration, producing compounds with the unappealing odors we associate with armpits and sweaty feet. One such compound is butanedione (above).

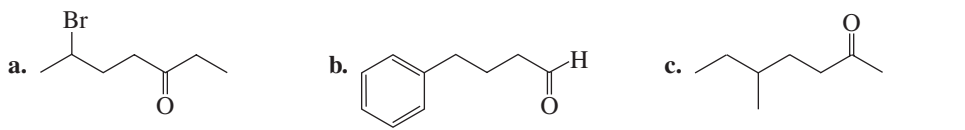
PROBLEM 1

Draw the structure for each of the following:

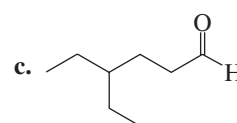
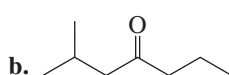
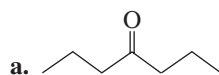
a. 3-hexanone **b.** β-methylbutyraldehyde **c.** isopropyl propyl ketone

PROBLEM 2

Name the following compounds:

a. Br O **b.** H O **c.** O

PROBLEM 3♦

Give two names for each of the following compounds:

a. **b.** **c.**

PROBLEM 4♦

Why are numbers not used to designate the position of the functional group in propanone and butanedione?

12.2 THE RELATIVE REACTIVITIES OF CARBONYL COMPOUNDS

formaldehyde

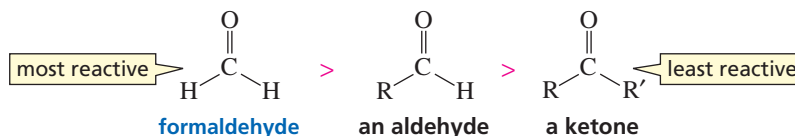
acetaldehyde

acetone

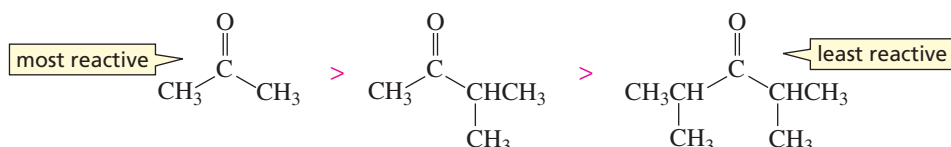
Aldehydes are more reactive than ketones.

We have seen that the carbonyl group is polar, because oxygen is more electronegative than carbon, so oxygen has a greater share of the double bond's electrons (Section 11.4). As a result, the carbonyl carbon is electron deficient (it is an electrophile), so it reacts with nucleophiles. The electron deficiency of the carbonyl carbon is indicated by the blue region in the electrostatic potential maps.

An aldehyde has a greater partial positive charge on its carbonyl carbon than a ketone does, because a hydrogen is more electron withdrawing than an alkyl group (Section 6.2). An aldehyde, therefore, is more reactive than a ketone toward nucleophilic addition. Steric factors also contribute to the greater reactivity of an aldehyde. The carbonyl carbon of an aldehyde is more accessible to a nucleophile, because the hydrogen attached to the carbonyl carbon of an aldehyde is smaller than the second alkyl group attached to the carbonyl carbon of a ketone.

relative reactivities

For the same reason, ketones with small alkyl groups bonded to the carbonyl carbon are more reactive than those with large alkyl groups.

relative reactivities

most reactive CH_3COCH_3 > $CH_3COCH(CH_3)CH_3$ > $CH_3CH(CH_3)COCH(CH_3)CH_3$ least reactive

PROBLEM 5♦

Which ketone in each pair is more reactive?

a. 2-heptanone or 4-heptanone

b. bromomethyl phenyl ketone or chloromethyl phenyl ketone

How does the reactivity of an aldehyde or a ketone toward nucleophiles compare with the reactivity of the carbonyl compounds whose reactions you studied in Chapter 11? Aldehydes and ketones are in the middle—they are *less* reactive than acyl halides and anhydrides, but they are *more* reactive than esters, carboxylic acids, and amides.

Aldehydes and ketones are less reactive than acyl chlorides and acid anhydrides, but they are more reactive than esters, carboxylic acids, and amides.

relative reactivities of carbonyl compounds

acyl halide > acid anhydride > aldehyde > ketone > ester ~ carboxylic acid > amide > carboxylate ion

most reactive (acyl halide) … least reactive (carboxylate ion)

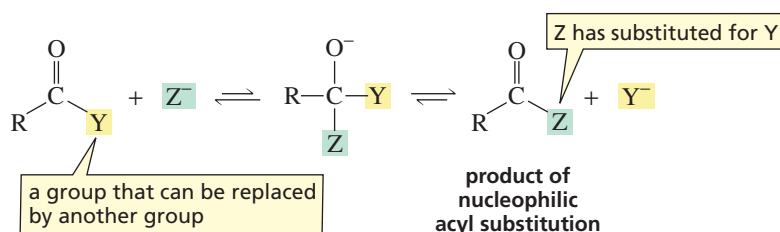
12.3 HOW ALDEHYDES AND KETONES REACT

In Section 11.5, we saw that the carbonyl group of a carboxylic acid or a carboxylic acid derivative is attached to a group that can be replaced by another group. Therefore, these compounds react with nucleophiles to form substitution products.

$$RC(=O)Y + Z^- \rightleftharpoons R-C(O^-)(Z)-Y \rightleftharpoons RC(=O)Z + Y^-$$

a group that can be replaced by another group

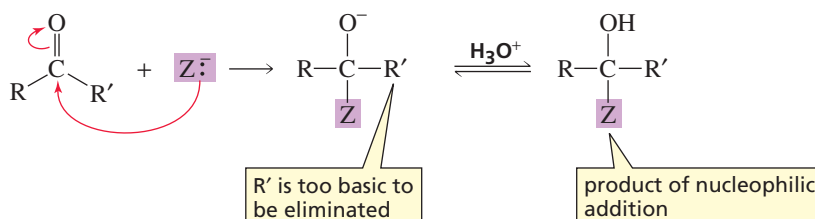
Z has substituted for Y

product of nucleophilic acyl substitution

Carboxylic acid derivatives undergo nucleophilic acyl substitution reactions.

In contrast, the carbonyl group of an aldehyde or a ketone is attached to a group that is too strong a base (H^- or R^-) to be eliminated under normal conditions, so it cannot be replaced by another group. Consequently, aldehydes and ketones react with nucleophiles to form addition products, not substitution products. Thus, aldehydes and ketones undergo **nucleophilic addition reactions,** whereas carboxylic acid derivatives undergo **nucleophilic acyl substitution reactions.** (Recall that a tetrahedral compound is unstable only if the sp^3 carbon is attached to an oxygen *and* to another electronegative atom; see Section 11.5).

$$RC(=O)R' + Z{:}^- \longrightarrow R-C(O^-)(Z)-R' \xrightleftharpoons{H_3O^+} R-C(OH)(Z)-R'$$

R′ is too basic to be eliminated

product of nucleophilic addition

Aldehydes and ketones undergo nucleophilic addition reactions.

12.4 ORGANOMETALLIC COMPOUNDS

We have seen that the compounds in Group III—alkyl halides, alcohols, ethers, and epoxides—contain a carbon that is bonded to a *more* electronegative atom. The carbon, therefore, is an *electrophile* and reacts with a nucleophile.

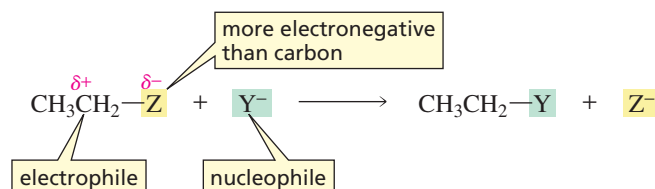
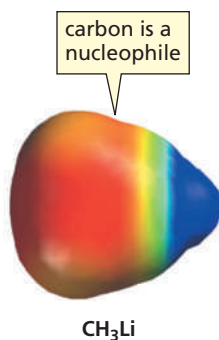
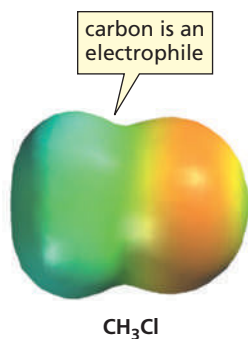
$$\overset{\delta+}{CH_3CH_2}-\overset{\delta-}{Z} + Y^- \longrightarrow CH_3CH_2-Y + Z^-$$

more electronegative than carbon

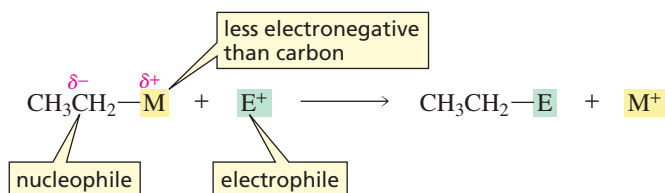
electrophile

nucleophile

CH_3Cl

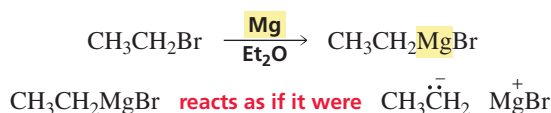
CH_3Li

A carbon is an electrophile if it is attached to a more electronegative atom.

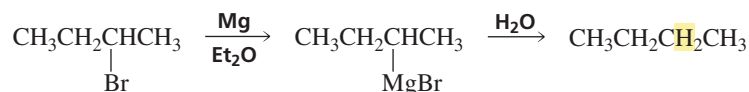
A carbon is a nucleophile if it is attached to a less electronegative atom.

But what if you wanted a carbon to be a *nucleophile* so it would react with an electrophile? To be a nucleophile, carbon would have to be bonded to a *less* electronegative atom.

Because metals are less electronegative than carbon (Table 1.3 on page 37), one way to create a nucleophilic carbon is to attach the carbon to a metal. A compound that contains a carbon–metal bond is called an **organometallic compound.** The electrostatic potential maps show that the carbon attached to the halogen in the alkyl halide is an electrophile (it is blue-green), whereas the carbon attached to the metal (Li) in the organometallic compound is a nucleophile (it is red).

The organometallic compounds known as **Grignard reagents** are the most widely used carbon nucleophiles. They are prepared by adding an alkyl halide to magnesium shavings being stirred in diethyl ether. This reaction inserts a magnesium between the carbon and the halogen. Grignard reagents react as if they were carbanions. Recall that a carbanion is a species containing a negatively charged carbon (Section 1.4).

$$CH_3CH_2Br \xrightarrow[Et_2O]{Mg} CH_3CH_2MgBr$$

CH_3CH_2MgBr reacts as if it were $CH_3\ddot{C}H_2^{-}\ \ \overset{+}{M}gBr$

Grignard reagents are such good nucleophiles (that is, such strong bases) that they will react immediately with any acid that is present in the reaction mixture—even with trace amounts of very weak acids such as water, alcohols, and amines. When this happens, the Grignard reagent is converted into an alkane.

$$\underset{\displaystyle |\atop Br}{CH_3CH_2CHCH_3} \xrightarrow[Et_2O]{Mg} \underset{\displaystyle |\atop MgBr}{CH_3CH_2CHCH_3} \xrightarrow{H_2O} CH_3CH_2CH_2CH_3$$

This means that Grignard reagents cannot be prepared from compounds that contain acidic groups (such as OH, NH_2, NHR, SH, C≡CH, or COOH).

PROBLEM 6♦

What are the products of the following reactions?

a. $CH_3CH_2MgBr + H_2O \longrightarrow$

b. $CH_3CH_2MgBr + CH_3OH \longrightarrow$

c. $CH_3CH_2MgBr + CH_3NH_2 \longrightarrow$

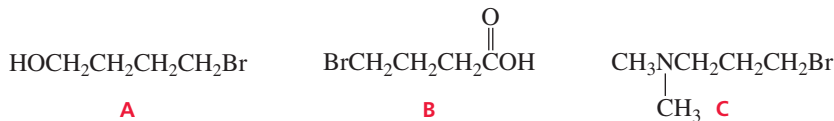
d. $CH_3MgBr + HC{\equiv}CH \longrightarrow$

PROBLEM 7♦

Which of the following alkyl halides could be successfully used to prepare a Grignard reagent?

A $HOCH_2CH_2CH_2CH_2Br$

B $BrCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$

C $CH_3\underset{\displaystyle |\atop CH_3}{N}CH_2CH_2CH_2Br$

12.5 THE REACTIONS OF CARBONYL COMPOUNDS WITH GRIGNARD REAGENTS

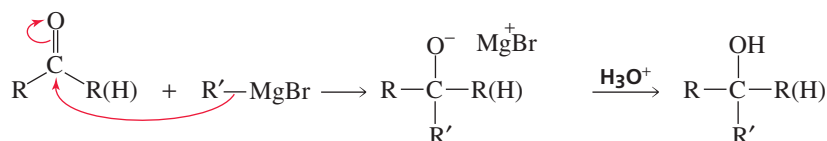
Reactions that result in the formation of new carbon–carbon bonds are very important to synthetic organic chemists when they need to synthesize large organic molecules from smaller molecules.

Addition of a Grignard reagent to a carbonyl compound is a versatile reaction that forms a new C—C bond. This reaction can produce compounds with a variety of structures because both the structure of the carbonyl compound and the structure of the Grignard reagent can be varied.

The Reactions of Aldehydes and Ketones with Grignard Reagents

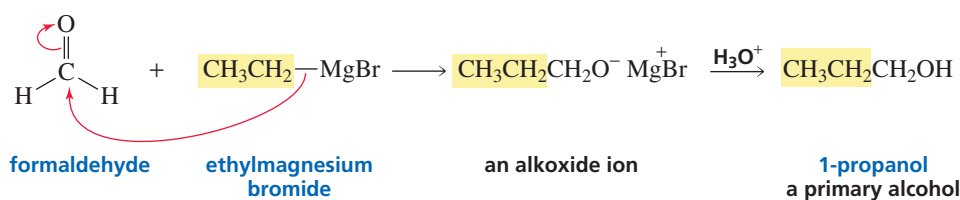
The reaction of an aldehyde or a ketone with a Grignard reagent is a nucleophilic addition reaction—the nucleophilic Grignard reagent adds to the carbonyl carbon. The tetrahedral alkoxide ion is stable, because it does not have a group that can be eliminated.

MECHANISM FOR THE REACTION OF AN ALDEHYDE OR A KETONE WITH A GRIGNARD REAGENT

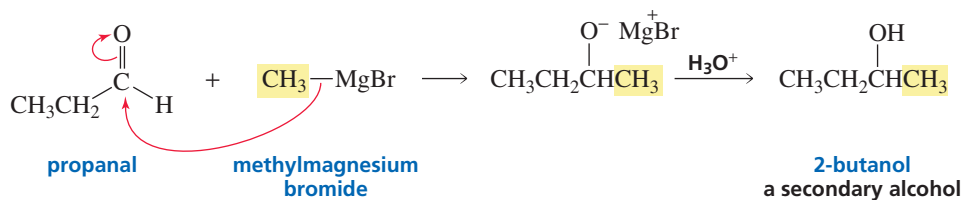
$$R-C(=O)-R(H) + R'-MgBr \longrightarrow R-C(O^-\ \overset{+}{Mg}Br)(R')-R(H) \xrightarrow{H_3O^+} R-C(OH)(R')-R(H)$$

- Nucleophilic addition of the Grignard reagent to the carbonyl carbon forms an alkoxide ion that is complexed with the magnesium ion.
- Addition of dilute acid breaks up the complex.

When a Grignard reagent reacts with formaldehyde, the product of the nucleophilic addition reaction is a *primary alcohol*.

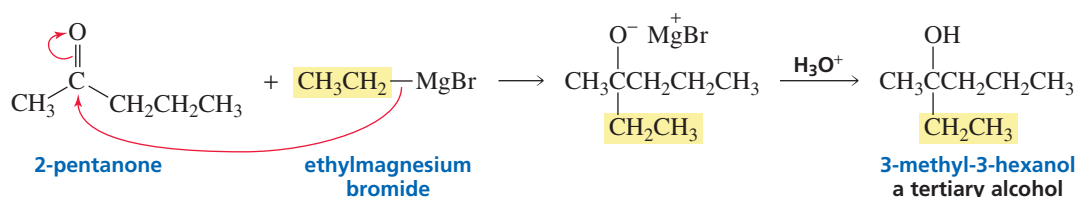
$$H-C(=O)-H + CH_3CH_2-MgBr \longrightarrow CH_3CH_2CH_2O^-\ \overset{+}{Mg}Br \xrightarrow{H_3O^+} CH_3CH_2CH_2OH$$

formaldehyde | ethylmagnesium bromide | an alkoxide ion | 1-propanol, a primary alcohol

When a Grignard reagent reacts with an aldehyde other than formaldehyde, the product of the nucleophilic addition reaction is a *secondary alcohol*.

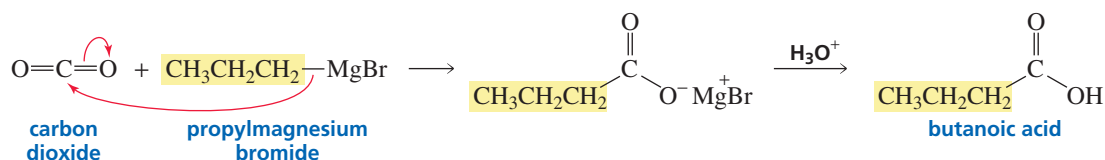
$$CH_3CH_2-C(=O)-H + CH_3-MgBr \longrightarrow CH_3CH_2CH(O^-\ \overset{+}{Mg}Br)CH_3 \xrightarrow{H_3O^+} CH_3CH_2CH(OH)CH_3$$

propanal | methylmagnesium bromide | 2-butanol, a secondary alcohol

When a Grignard reagent reacts with a ketone, the product of the nucleophilic addition reaction is a *tertiary alcohol*.

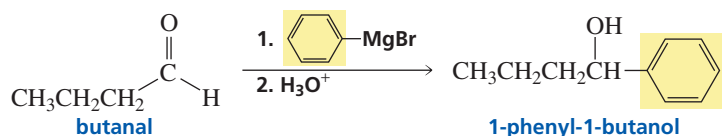
$$CH_3-C(=O)-CH_2CH_2CH_3 + CH_3CH_2-MgBr \longrightarrow CH_3C(O^-\ \overset{+}{Mg}Br)(CH_2CH_3)CH_2CH_2CH_3 \xrightarrow{H_3O^+} CH_3C(OH)(CH_2CH_3)CH_2CH_2CH_3$$

2-pentanone | ethylmagnesium bromide | 3-methyl-3-hexanol, a tertiary alcohol

A Grignard reagent can also react with carbon dioxide. The product of the reaction is a carboxylic acid that has one more carbon than the Grignard reagent.

$$O{=}C{=}O + CH_3CH_2CH_2{-}MgBr \longrightarrow CH_3CH_2CH_2C(=O)O^- \overset{+}{Mg}Br \xrightarrow{H_3O^+} CH_3CH_2CH_2C(=O)OH$$

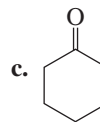
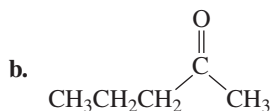
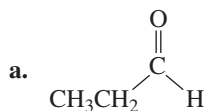
carbon dioxide — propylmagnesium bromide — butanoic acid

In the following reaction, the reagents above and below the reaction arrows are numbered in order of use, indicating that the acid is not added until after the Grignard reagent has reacted with the carbonyl compound.

$$CH_3CH_2CH_2C(=O)H \xrightarrow[\text{2. } H_3O^+]{\text{1. } C_6H_5MgBr} CH_3CH_2CH_2CH(OH){-}C_6H_5$$

butanal — 1-phenyl-1-butanol

If the reaction with the carbonyl compound forms a product with an asymmetric center, such as the preceding reaction that forms 1-phenyl-1-butanol, the product will be a racemic mixture. (Recall that when a reactant without an asymmetric center undergoes a reaction that forms an asymmetric center, the product will be a racemic mixture; Section 6.5.)

PROBLEM 8♦

What products are formed when the following compounds react with CH_3MgBr, followed by the addition of dilute acid? Disregard stereoisomers.

a. $CH_3CH_2C(=O)H$ **b.** $CH_3CH_2CH_2C(=O)CH_3$ **c.** cyclohexanone

PROBLEM 9♦

We saw on page 465 that 3-methyl-3-hexanol can be synthesized from the reaction of 2-pentanone with ethylmagnesium bromide. What other combinations of ketone and Grignard reagent could be used to prepare the same tertiary alcohol?

PROBLEM 10♦

a. How many stereoisomers are obtained from the reaction of 2-pentanone with ethylmagnesium bromide followed by the addition of dilute acid?

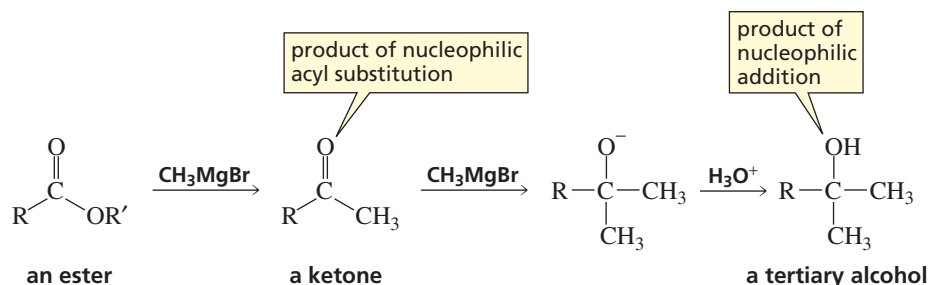
b. How many stereoisomers are obtained from the reaction of 2-pentanone with methylmagnesium bromide followed by the addition of dilute acid?

The Reactions of Esters and Acyl Chlorides with Grignard Reagents

In addition to reacting with aldehydes and ketones, Grignard reagents also react with esters and acyl chlorides, compounds you studied in Chapter 11. Esters and acyl chlorides undergo two successive reactions with the Grignard reagent. The first reaction is a *nucleophilic acyl substitution reaction* because an ester or an acyl chloride, unlike an aldehyde or a ketone, has a group that can be replaced by the alkyl fragment of the Grignard reagent (Section 11.5). The second reaction is a *nucleophilic addition reaction*.

product of nucleophilic acyl substitution

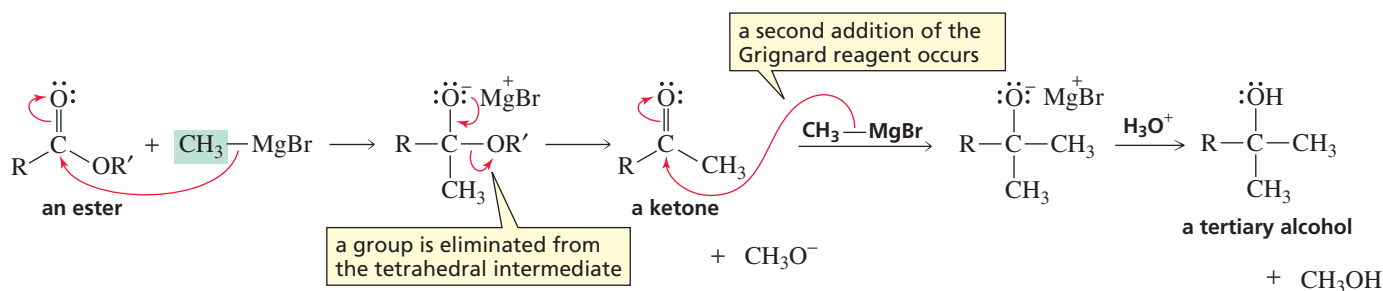
product of nucleophilic addition

$$\underset{\text{an ester}}{R-\overset{O}{\overset{\|}{C}}-OR'} \xrightarrow{CH_3MgBr} \underset{\text{a ketone}}{R-\overset{O}{\overset{\|}{C}}-CH_3} \xrightarrow{CH_3MgBr} R-\overset{O^-}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-CH_3 \xrightarrow{H_3O^+} \underset{\text{a tertiary alcohol}}{R-\overset{OH}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-CH_3}$$

The product of the reaction of an ester with a Grignard reagent is a tertiary alcohol. Because the tertiary alcohol is formed from two successive reactions with the Grignard reagent, the alcohol has at least two identical alkyl groups bonded to the tertiary carbon.

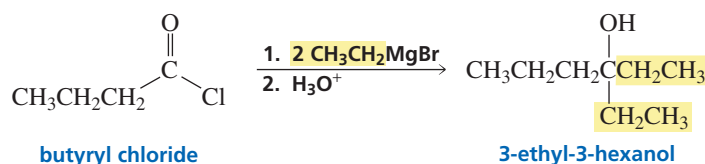
MECHANISM FOR THE REACTION OF AN ESTER WITH A GRIGNARD REAGENT

$$\underset{\text{an ester}}{R-\overset{:\ddot{O}:}{\overset{\|}{C}}-OR'} + CH_3-MgBr \longrightarrow R-\overset{:\ddot{O}:^-\ \overset{+}{Mg}Br}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-OR' \longrightarrow \underset{\text{a ketone}}{R-\overset{:\ddot{O}:}{\overset{\|}{C}}-CH_3} + CH_3O^- \xrightarrow{CH_3-MgBr} R-\overset{:\ddot{O}:^-\ \overset{+}{Mg}Br}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-CH_3 \xrightarrow{H_3O^+} \underset{\text{a tertiary alcohol}}{R-\overset{:\ddot{O}H}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-CH_3} + CH_3OH$$

a group is eliminated from the tetrahedral intermediate

a second addition of the Grignard reagent occurs

- Nucleophilic addition of the Grignard reagent to the carbonyl carbon forms a tetrahedral intermediate that is unstable because it has a group that can be eliminated.
- The tetrahedral intermediate eliminates the alkoxide ion, forming a ketone.
- The ketone reacts with a second molecule of the Grignard reagent, forming an alkoxide ion that forms a tertiary alcohol upon protonation.

Tertiary alcohols are also formed from the reaction of two equivalents of a Grignard reagent with an acyl chloride. The mechanism for the reaction of a Grignard reagent with an acyl chloride is the same as the mechanism for the reaction of a Grignard reagent with an ester.

$$\underset{\text{butyryl chloride}}{CH_3CH_2CH_2-\overset{O}{\overset{\|}{C}}-Cl} \xrightarrow[\text{2. } H_3O^+]{\text{1. } 2\ CH_3CH_2MgBr} \underset{\text{3-ethyl-3-hexanol}}{CH_3CH_2CH_2\overset{OH}{\overset{|}{\underset{CH_2CH_3}{\underset{|}{C}}}}CH_2CH_3}$$

Synthesizing Organic Compounds

a spotted owl (*Strix occidentalis*) taking off from a falconer's glove

Organic chemists synthesize compounds for many reasons: to study their properties, to answer a variety of chemical questions, or to take advantage of one or more useful properties. One reason chemists synthesize a natural product—that is, a compound synthesized in nature—is to provide a larger supply of the compound than nature can produce. For example, Taxol—a compound that has successfully treated ovarian cancer, breast cancer, and certain forms of lung cancer by inhibiting mitosis—is extracted from the bark of *Taxus*, a yew tree found in the Pacific Northwest. The supply of natural Taxol is limited because yew trees are uncommon, they grow very slowly, and stripping the bark kills the tree. Moreover, the bark of a 40-foot tree, which may have taken 200 years to grow, provides only 0.5 g of the drug. In addition, *Taxus* forests serve as habitats for the spotted owl, an endangered species, so harvesting the trees would accelerate the owl's demise. Once chemists determined the structure of Taxol, efforts were undertaken to synthesize it in order to make it more widely available as an anticancer drug. Several syntheses have been successful.

yew tree bark

Taxol®

Once a compound has been synthesized, chemists can study its properties to learn how it works. Then, they may be able to design and synthesize analogues to obtain safer or more potent drugs (Section 9.10).

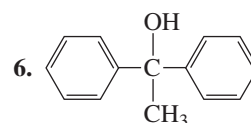
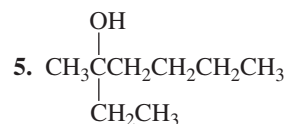
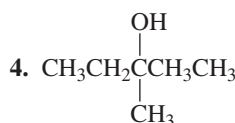
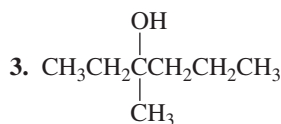
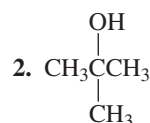
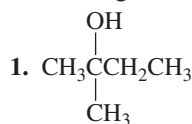
Semisynthetic Drugs

Taxol is difficult to synthesize because of its many functional groups and 11 asymmetric centers. The synthesis is a lot easier if the common English yew shrub carries out the first part of the synthesis. A precursor of the drug is extracted from the shrub's needles, and then the precursor is converted to Taxol in a four-step procedure in the laboratory. Thus, the precursor is isolated from a renewable resource, whereas the drug itself could be obtained only by killing a slow-growing tree. This is an example of how chemists have learned to synthesize compounds jointly with nature.

a yew shrub

PROBLEM 11 Solved

a. Which of the following tertiary alcohols cannot be prepared by the reaction of an ester with excess Grignard reagent?

1. $CH_3C(OH)(CH_3)CH_2CH_3$
2. $CH_3C(OH)(CH_3)CH_3$
3. $CH_3CH_2C(OH)(CH_3)CH_2CH_2CH_3$
4. $CH_3CH_2C(OH)(CH_3)CH_2CH_3$
5. $CH_3C(OH)(CH_2CH_3)CH_2CH_2CH_2CH_3$
6. $(C_6H_5)_2C(OH)CH_3$

b. For those alcohols that can be prepared by the reaction of an ester with excess Grignard reagent, what ester and what Grignard reagent should be used?

Solution to 11a A tertiary alcohol prepared by the reaction of an ester with two equivalents of a Grignard reagent must have at least two identical substituents bonded to the carbon to which the OH is attached, because two of the three substituents come from the Grignard reagent. Alcohols 3 and 5 do not have two identical substituents, so they cannot be prepared in this way.

Solution to 11b (1) An ester of propanoic acid and excess methylmagnesium bromide.

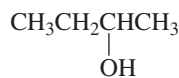
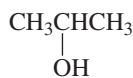
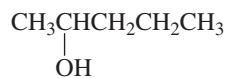
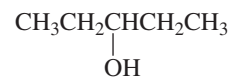
PROBLEM 12♦

Which of the following secondary alcohols can be prepared by the reaction of methyl formate with excess Grignard reagent?

A. $CH_3CH_2CH(OH)CH_3$

B. $CH_3CH(OH)CH_3$

C. $CH_3CH(OH)CH_2CH_2CH_3$

D. $CH_3CH_2CH(OH)CH_2CH_3$

PROBLEM 13

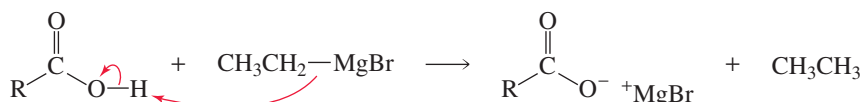
Write the mechanism for the reaction of acetyl chloride with two equivalents of ethylmagnesium bromide.

PROBLEM-SOLVING STRATEGY

Predicting the Products of a Reaction with a Grignard Reagent

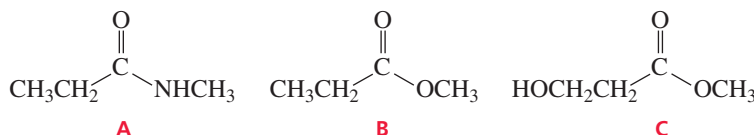
Why doesn't a Grignard reagent add to the carbonyl carbon of a carboxylic acid?

We know that Grignard reagents add to carbonyl carbons, so if we find that a Grignard reagent does not add to the carbonyl carbon, we can conclude that it must react more rapidly with another part of the molecule. A carboxylic acid has an acidic proton that reacts rapidly with the Grignard reagent, converting it to an alkane.

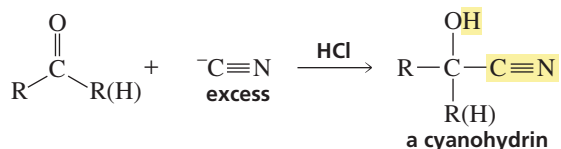
$$RC(=O)OH + CH_3CH_2-MgBr \longrightarrow RC(=O)O^- \; ^+MgBr + CH_3CH_3$$

Now use the strategy you have just learned to solve Problem 14.

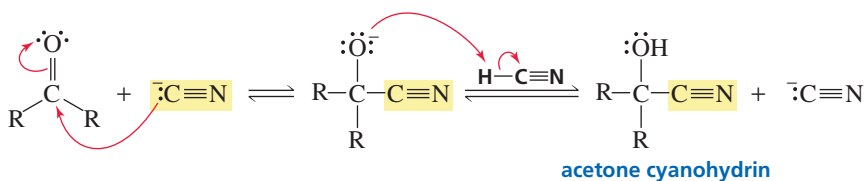
PROBLEM 14♦

Which of the following compounds will not undergo a nucleophilic addition reaction with one equivalent of a Grignard reagent?

$CH_3CH_2C(=O)NHCH_3$ **A** $\quad CH_3CH_2C(=O)OCH_3$ **B** $\quad HOCH_2CH_2C(=O)OCH_3$ **C**

12.6 THE REACTIONS OF ALDEHYDES AND KETONES WITH CYANIDE ION

Cyanide ion is another carbon nucleophile that can add to an aldehyde or a ketone. The product of the reaction is a **cyanohydrin**. Excess cyanide ion is used to ensure that HCl does not convert all the cyanide ion to HCN, so some cyanide ion is available to act as a nucleophile.

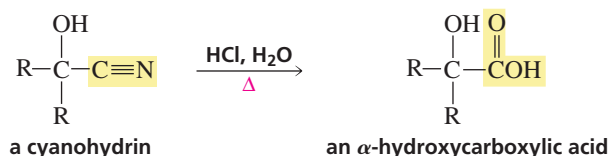
$$RC(=O)R(H) + \underset{\text{excess}}{^-C{\equiv}N} \xrightarrow{\text{HCl}} \underset{\text{a cyanohydrin}}{R-C(OH)(R(H))-C{\equiv}N}$$

MECHANISM FOR THE REACTION OF AN ALDEHYDE OR KETONE WITH HYDROGEN CYANIDE

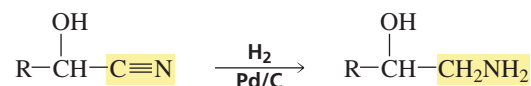
$$RC(=O)R + {:}C{\equiv}N^- \rightleftharpoons R-C(O^-)(R)-C{\equiv}N \xrightleftharpoons{H-C{\equiv}N} \underset{\text{acetone cyanohydrin}}{R-C(OH)(R)-C{\equiv}N} + {}^-{:}C{\equiv}N$$

- Cyanide ion adds to the carbonyl carbon.
- The alkoxide ion is protonated by an undissociated molecule of hydrogen cyanide.

The addition of hydrogen cyanide to aldehydes and ketones is a synthetically useful reaction because of the subsequent reactions that can be carried out on the cyanohydrin.

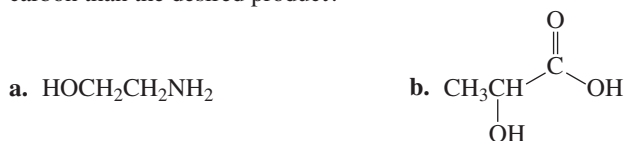
For example, the acid-catalyzed hydrolysis of a cyanohydrin forms an α-hydroxycarboxylic acid (Section 11.13).

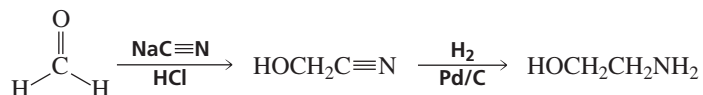
$$R-\overset{OH}{\underset{R}{C}}-C{\equiv}N \xrightarrow[\Delta]{HCl,\ H_2O} R-\overset{OH}{\underset{R}{C}}-\overset{O}{\overset{\|}{C}}OH$$

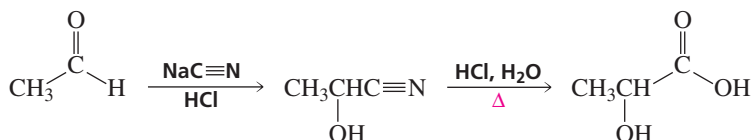
a cyanohydrin — an α-hydroxycarboxylic acid

The catalytic addition of two equivalents of hydrogen to the triple bond of a cyanohydrin produces a primary amine with an OH group on the β-carbon.

$$R-\overset{OH}{CH}-C{\equiv}N \xrightarrow[Pd/C]{H_2} R-\overset{OH}{CH}-CH_2NH_2$$

PROBLEM 15 Solved

How can the following compounds be prepared from a carbonyl compound that has one fewer carbon than the desired product?

a. $HOCH_2CH_2NH_2$ **b.** $CH_3\underset{OH}{CH}\overset{O}{\overset{\|}{C}}OH$

Solution to 15a The starting material for the synthesis of this two-carbon compound must be formaldehyde, a one-carbon compound. Addition of hydrogen cyanide followed by addition of H_2 to the triple bond of the cyanohydrin forms the target molecule.

$$H\overset{O}{\overset{\|}{C}}H \xrightarrow[HCl]{NaC{\equiv}N} HOCH_2C{\equiv}N \xrightarrow[Pd/C]{H_2} HOCH_2CH_2NH_2$$

Solution to 15b The addition of cyanide ion adds one carbon to the reactant, so the starting material for the synthesis of this three-carbon α-hydroxycarboxylic acid must be acetaldehyde, a two-carbon compound. Addition of hydrogen cyanide, followed by hydrolysis of the resulting cyanohydrin, forms the target molecule.

$$CH_3\overset{O}{\overset{\|}{C}}H \xrightarrow[HCl]{NaC{\equiv}N} CH_3\underset{OH}{CH}C{\equiv}N \xrightarrow[\Delta]{HCl,\ H_2O} CH_3\underset{OH}{CH}\overset{O}{\overset{\|}{C}}OH$$

PROBLEM 16

Show two ways to convert an alkyl halide into a carboxylic acid that has one more carbon than the alkyl halide.

12.7 THE REACTIONS OF CARBONYL COMPOUNDS WITH HYDRIDE ION

The Reactions of Aldehydes and Ketones with Hydride Ion

A hydride ion is another strongly basic nucleophile that reacts with an aldehyde or a ketone to form a nucleophilic addition product. Usually, sodium borohydride ($NaBH_4$) is used for the source of the hydride ion.

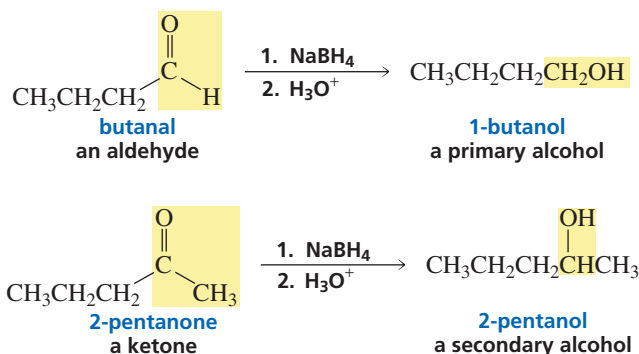
$$CH_3CH_2CH_2C(=O)H \xrightarrow[2.\ H_3O^+]{1.\ NaBH_4} CH_3CH_2CH_2CH_2OH$$

butanal
an aldehyde

1-butanol
a primary alcohol

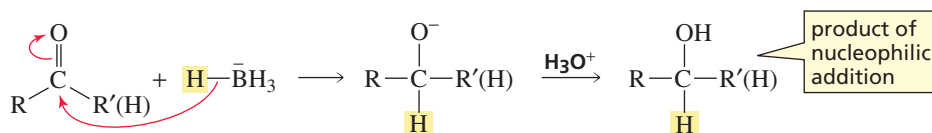
$$CH_3CH_2CH_2C(=O)CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NaBH_4} CH_3CH_2CH_2CH(OH)CH_3$$

2-pentanone
a ketone

2-pentanol
a secondary alcohol

Recall that the addition of hydrogen to a compound is a **reduction reaction** (Section 5.6). *Aldehydes* are reduced to *primary alcohols*, and *ketones* are reduced to *secondary alcohols*. Notice that the acid is not added to the reaction mixture until after the hydride ion has reacted with the carbonyl compound.

MECHANISM FOR THE REACTION OF AN ALDEHYDE OR A KETONE WITH HYDRIDE ION

$$RC(=O)R'(H) + H-\bar{B}H_3 \longrightarrow R-C(O^-)(H)-R'(H) \xrightarrow{H_3O^+} R-C(OH)(H)-R'(H)$$

product of nucleophilic addition

- Addition of a hydride ion to the carbonyl carbon of an aldehyde or a ketone forms an alkoxide ion.
- Protonation by a dilute acid forms an alcohol.

PROBLEM 17♦

What alcohols are obtained from the reduction of the following compounds with sodium borohydride?

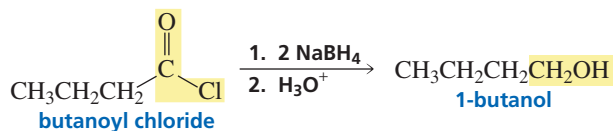
a. 2-methylpropanal
b. cyclohexanone
c. 4-*tert*-butylcyclohexanone
d. methyl phenyl ketone

The Reactions of Acyl Chlorides with Hydride Ion

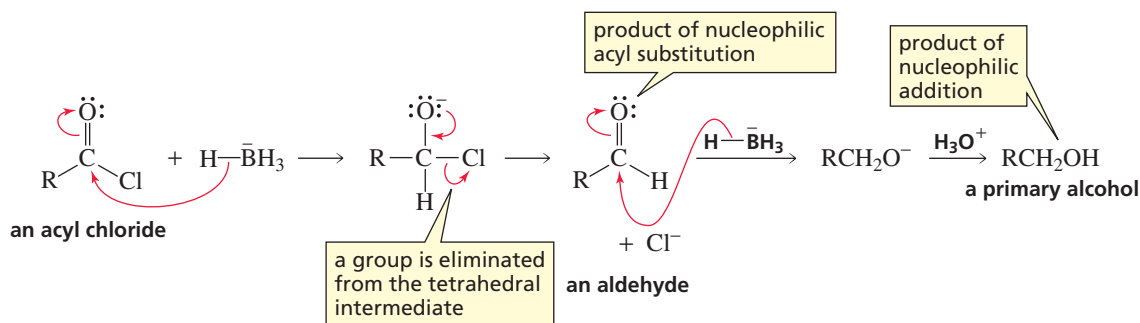
Because an acyl chloride has a group that can be replaced by another group, it undergoes two successive reactions with hydride ion, just as it undergoes two successive reactions with a Grignard reagent (Section 12.5). Therefore, the reaction of an acyl chloride with sodium borohydride forms a primary alcohol with the same number of carbons as the acyl chloride.

$$CH_3CH_2CH_2C(=O)Cl \xrightarrow[2.\ H_3O^+]{1.\ 2\ NaBH_4} CH_3CH_2CH_2CH_2OH$$

butanoyl chloride

1-butanol

MECHANISM FOR THE REACTION OF AN ACYL CHLORIDE WITH HYDRIDE ION

$$RC(=O)Cl + H{-}\bar{B}H_3 \longrightarrow R{-}C(O^-)(H){-}Cl \longrightarrow RC(=O)H + Cl^- \xrightarrow{H{-}\bar{B}H_3} RCH_2O^- \xrightarrow{H_3O^+} RCH_2OH$$

an acyl chloride; a group is eliminated from the tetrahedral intermediate; an aldehyde (product of nucleophilic acyl substitution); a primary alcohol (product of nucleophilic addition)

- The acyl chloride undergoes a nucleophilic acyl substitution reaction because it has a group (Cl^-) that can be replaced by hydride ion. The product of this reaction is an aldehyde.
- The aldehyde undergoes a nucleophilic addition reaction with a second equivalent of hydride ion, forming an alkoxide ion.
- Protonation of the alkoxide ion forms a primary alcohol.

The Reactions of Esters and Carboxylic Acids with Hydride Ion

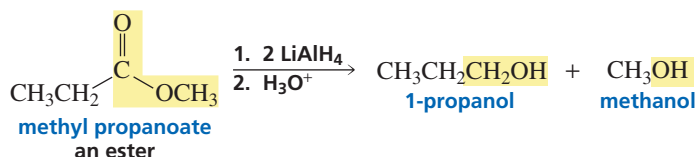
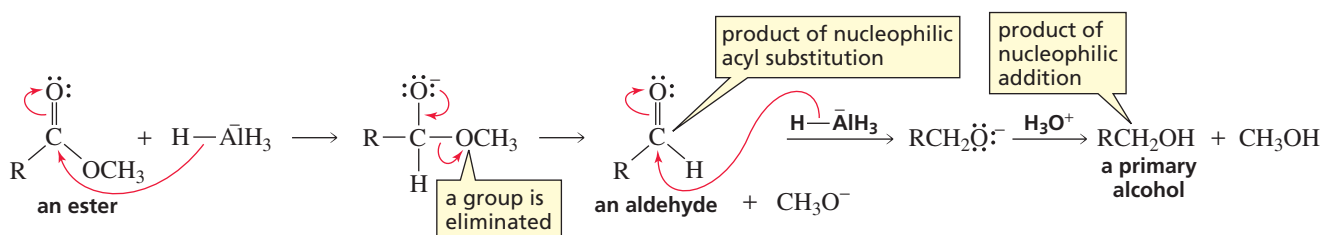
Sodium borohydride ($NaBH_4$) is not a sufficiently strong hydride donor to react with carbonyl compounds that are less reactive than aldehydes and ketones. Therefore, esters, carboxylic acids, and amides must be reduced with lithium aluminum hydride ($LiAlH_4$), a more reactive hydride donor. Lithium aluminum hydride is not as safe or as easy to use as sodium borohydride, so it is never used if $NaBH_4$ can be used instead.

The reaction of an ester with $LiAlH_4$ produces two alcohols, a primary alcohol that corresponds to the acyl portion of the ester and an alcohol that corresponds to the leaving group.

$$CH_3CH_2C(=O)OCH_3 \xrightarrow[\text{2. } H_3O^+]{\text{1. 2 } LiAlH_4} CH_3CH_2CH_2OH + CH_3OH$$

methyl propanoate (an ester) → 1-propanol + methanol

MECHANISM FOR THE REACTION OF AN ESTER WITH HYDRIDE ION

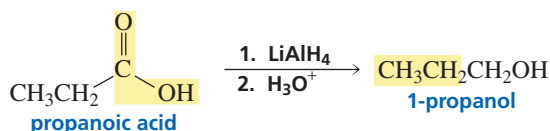
$$RC(=O)OCH_3 + H{-}\bar{A}lH_3 \longrightarrow R{-}C(O^-)(H){-}OCH_3 \longrightarrow RC(=O)H + CH_3O^- \xrightarrow{H{-}\bar{A}lH_3} RCH_2O^- \xrightarrow{H_3O^+} RCH_2OH + CH_3OH$$

an ester; a group is eliminated; an aldehyde (product of nucleophilic acyl substitution); a primary alcohol (product of nucleophilic addition)

- The ester undergoes a nucleophilic acyl substitution reaction because an ester has a group (CH_3O^-) that can be replaced by hydride ion. The product of this reaction is an aldehyde.
- The aldehyde undergoes a nucleophilic addition reaction with a second equivalent of hydride ion, forming an alkoxide ion.
- Protonation of the two alkoxide ions forms two alcohols.

Acyl chlorides and esters undergo two successive reactions with hydride ion and with Grignard reagents.

The reaction of an ester with hydride ion cannot be stopped at the aldehyde, because an aldehyde is more reactive than an ester (Section 12.2).

The reaction of a carboxylic acid with hydride ion forms a primary alcohol with the same number of carbons as the carboxylic acid.

$$CH_3CH_2C(=O)OH \xrightarrow[\text{2. } H_3O^+]{\text{1. } LiAlH_4} CH_3CH_2CH_2OH$$

propanoic acid → 1-propanol

The reaction of a carboxylic acid with $LiAlH_4$ forms a primary alcohol.

PROBLEM 18♦

What products would be obtained from the reaction of the following compounds with $LiAlH_4$ followed by treatment with dilute acid?

a. ethyl butanoate **b.** methyl benzoate **c.** pentanoic acid

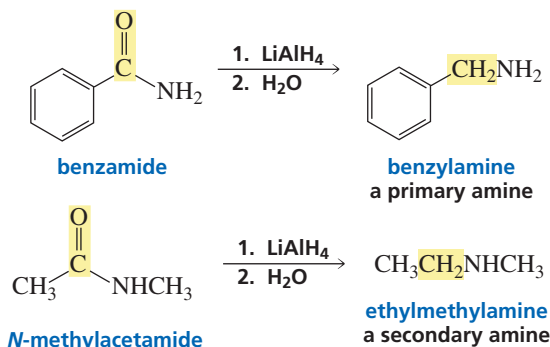
The Reactions of Amides with Hydride Ion

Amides also undergo two successive additions of hydride ion when they react with $LiAlH_4$. Overall, the reaction converts a carbonyl group into a methylene (CH_2) group, so the product of the reaction is an amine. Primary, secondary, or tertiary amines can be formed, depending on the number of substituents bonded to the nitrogen of the amide. (Notice that H_2O rather than H_3O^+ is used in the second step of the reaction. If H_3O^+ were used, the product would be a protonated amine.)

$$C_6H_5C(=O)NH_2 \xrightarrow[\text{2. } H_2O]{\text{1. } LiAlH_4} C_6H_5CH_2NH_2$$

benzamide → benzylamine, a primary amine

$$CH_3C(=O)NHCH_3 \xrightarrow[\text{2. } H_2O]{\text{1. } LiAlH_4} CH_3CH_2NHCH_3$$

N-methylacetamide → ethylmethylamine, a secondary amine

Biological reactions also need reagents that can deliver hydride ions to carbonyl groups. Cells use NADH and NADPH as hydride donors. (Sodium borohydride and lithium aluminum hydride are too reactive to be used in cells.) These hydride donors are discussed in Section 18.7.

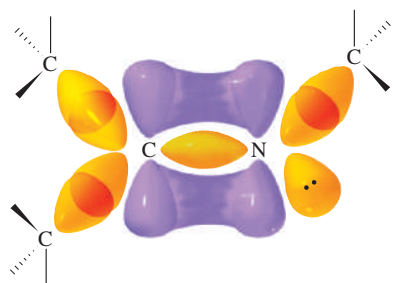
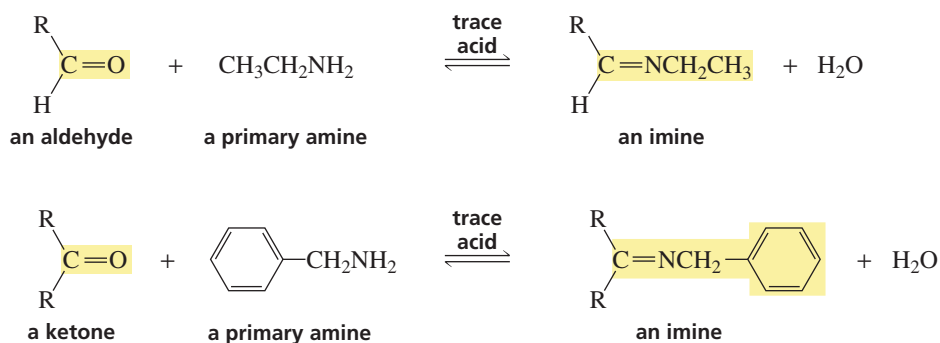
PROBLEM 19♦

What amides would you react with $LiAlH_4$ to form the following amines?

a. benzylmethylamine **b.** ethylamine **c.** diethylamine **d.** triethylamine

12.8 THE REACTIONS OF ALDEHYDES AND KETONES WITH AMINES

Aldehydes and Ketones Form Imines with Primary Amines

An aldehyde or a ketone reacts with a *primary* amine to form an imine (sometimes called a **Schiff base**). An **imine** is a compound with a carbon–nitrogen double bond. The reaction requires a trace amount of acid. Notice that imine formation replaces a C═O with a C═NR.

▲ **Figure 12.1**
Bonding in an imine. The π bond is formed by side-to-side overlap of a *p* orbital of carbon with a *p* orbital of nitrogen; it is perpendicular to the orange orbitals.

A C═N group (Figure 12.1) is similar to a C═O group (Figure 11.1 on page 426). The imine nitrogen is sp^2 hybridized. One of its sp^2 orbitals forms a σ bond with the imine carbon, one forms a σ bond with a substituent, and the third sp^2 orbital contains a lone pair. The *p* orbital of nitrogen and the *p* orbital of carbon overlap to form a π bond.

The mechanism for imine formation is shown next. Because the addition of the amine is followed by the elimination of water, the reaction is a **nucleophilic addition-elimination reaction.** (Recall that HB^+ represents any species in the solution that is capable of donating a proton, and :B represents any species in the solution that is capable of removing a proton.)

MECHANISM FOR IMINE FORMATION

Imine formation replaces a C═O with a C═NR.

H—B⁺ ; O: + RNH₂ ⇌ :Ö:⁻ NH₂R⁺ ⇌ :OH ⁺NHR ⇌ :OH NHR

nucleophile adds to the carbonyl carbon

N–protonated carbinolamine

:B

neutral tetrahedral intermediate
a carbinolamine

O–protonated carbinolamine

elimination of water

=NR ⇌ =N⁺R H + H₂O ⇌ H :O⁺H NHR

HB⁺

an imine

a protonated imine

removal of a proton

Notice that the pattern of three tetrahedral intermediates that we saw in the acid-catalyzed mechanisms in Chapter 11 also occurs in this mechanism:

protonated tetrahedral intermediate ⇌ neutral tetrahedral intermediate ⇌ protonated tetrahedral intermediate.

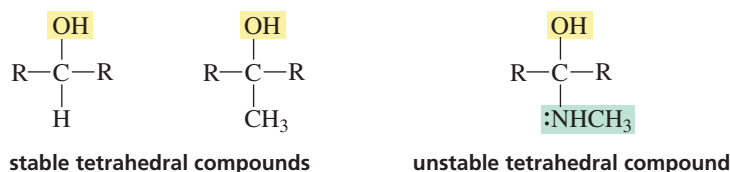
- The amine adds to the carbonyl carbon.
- Protonation of the alkoxide ion and deprotonation of the ammonium ion form a neutral tetrahedral intermediate.
- The neutral tetrahedral intermediate, called a *carbinolamine*, is in equilibrium with two protonated forms because either its oxygen (forward step) or its nitrogen (reverse step) can be protonated.
- Because the tetrahedral intermediate is unstable, water is eliminated from the oxygen-protonated intermediate, thereby forming a protonated imine.
- A base removes a proton from the nitrogen to form the imine.

Aldehydes and ketones react with primary amines to form imines.

Unlike the stable tetrahedral compounds that are formed when a Grignard reagent or a hydride ion adds to an aldehyde or a ketone, the tetrahedral compound formed when

an amine adds to an aldehyde or a ketone is unstable, because when its OH group is protonated, the lone pair on nitrogen can eliminate the water molecule.

$$\underset{\text{stable tetrahedral compounds}}{R-\overset{OH}{\underset{H}{C}}-R \qquad R-\overset{OH}{\underset{CH_3}{C}}-R} \qquad \underset{\text{unstable tetrahedral compound}}{R-\overset{OH}{\underset{:NHCH_3}{C}}-R}$$

stable tetrahedral compounds **unstable tetrahedral compound**

Imine formation is reversible. The nitrogen of the carbinolamine is more basic than the oxygen, so the equilibrium favors the nitrogen-protonated tetrahedral intermediate. However, the equilibrium can be forced toward the oxygen-protonated tetrahedral intermediate and, therefore, toward the imine, by removing water as it is formed.

Because imine formation is reversible, an imine can be hydrolyzed back to the carbonyl compound and the amine in an acidic solution. Notice that the amine product is protonated because it is in an acidic solution.

$$R_2C{=}NCH_2CH_3 + H_2O \xrightarrow{HCl} R_2C{=}O + CH_3CH_2\overset{+}{N}H_3$$

An imine undergoes acid-catalyzed hydrolysis to form a carbonyl compound and a protonated primary amine.

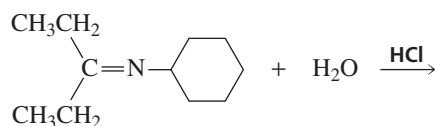
Imine formation and hydrolysis are important reactions in biological systems. For example, we will see that all the reactions that require vitamin B_6 involve imine formation (Section 18.11), and imine hydrolysis is the reason that DNA contains T nucleotides instead of U nucleotides (Section 21.10).

PROBLEM 20

What are the products of the following reactions? (A trace amount of acid is present in each case.)

a. cyclopentanone + ethylamine
b. cyclopentanone + cyclohexylamine
c. 3-pentanone + butylamine
d. 3-pentanone + cyclohexylamine

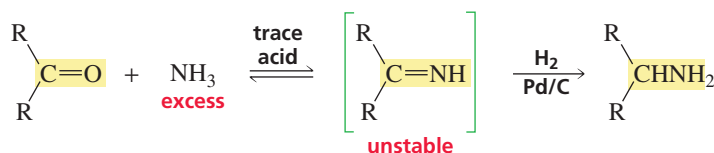
PROBLEM 21

What are the products of the following reaction?

$$(CH_3CH_2)_2C{=}N{-}C_6H_{11} + H_2O \xrightarrow{HCl}$$

Reductive Amination

The imine formed from the reaction of an aldehyde or a ketone with ammonia is relatively unstable, because it does not have a substituent other than a hydrogen attached to the nitrogen. Nevertheless, such an imine is a useful intermediate.

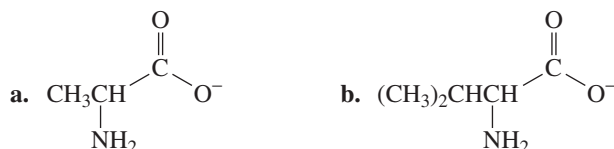
For example, if the reaction with ammonia is carried out in the presence of a reducing agent such as H_2 and a metal catalyst, then the double bond will be reduced as it is formed, forming a primary amine. The reaction of an aldehyde or a ketone with excess ammonia in the presence of a reducing agent is called **reductive amination.**

$$R_2C{=}O + NH_3 \text{ (excess)} \xrightleftharpoons{\text{trace acid}} [R_2C{=}NH] \text{ (unstable)} \xrightarrow[\text{Pd/C}]{H_2} R_2CHNH_2$$

The double bond of an imine is reduced more rapidly than the C═O bond, so reduction of the carbonyl group does not compete with reduction of the imine in these reactions.

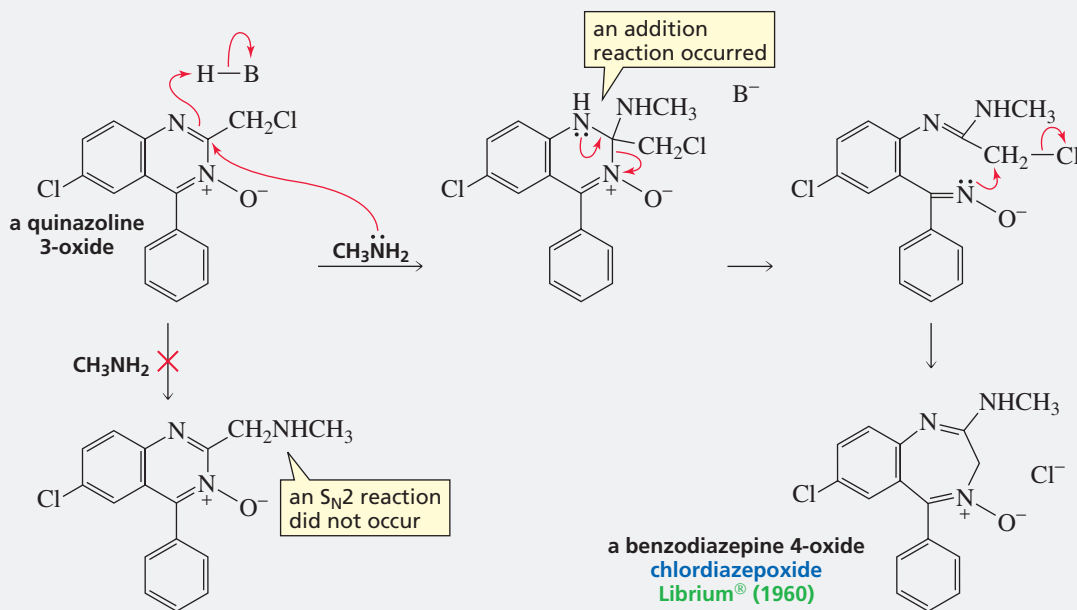
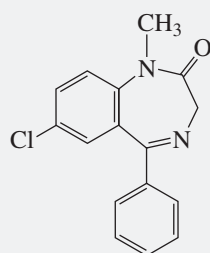
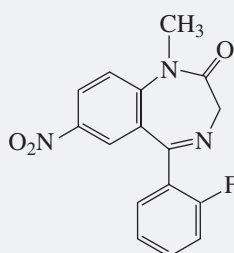
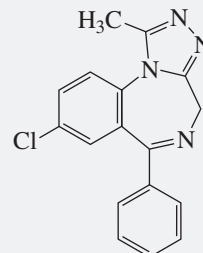
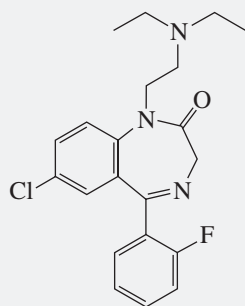
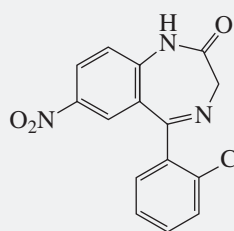
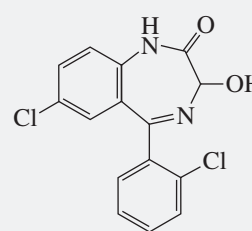
PROBLEM 22

The compounds commonly known as "amino acids" are actually α-aminocarboxylic acids (Section 17.0). What carbonyl compounds should be used to synthesize the two amino acids shown here?

a. $CH_3CH(NH_2)CO_2^-$

b. $(CH_3)_2CHCH(NH_2)CO_2^-$

Serendipity in Drug Development

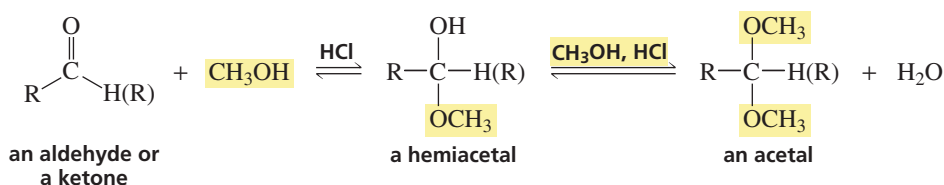
Many drugs have been discovered accidentally. Librium, a tranquilizer, is one example of such a drug. Leo Sternbach, a research chemist at Hoffmann-LaRoche, synthesized a series of quinazoline 3-oxides, but none of them showed any pharmacological activity. One of the compounds was not submitted for testing, because it was not the quinazoline 3-oxide Sternbach had set out to synthesize. Two years after the project was abandoned, a laboratory worker came across this compound while cleaning up the lab, and Sternbach decided that he might as well submit it for testing before it was thrown away. The compound was found to have tranquilizing properties and, when its structure was investigated, was discovered to be a benzodiazepine 4-oxide.

Methylamine, instead of displacing the chloro substituent in an S_N2 reaction to form a quinazoline 3-oxide, had added to the imine group of the six-membered ring. This caused the ring to open and then reclose in an S_N2 reaction to form a benzodiazepine. The compound was given the brand name Librium when it was put into clinical use in 1960.

Librium was structurally modified in an attempt to find other tranquilizers (Section 9.10). One successful modification produced Valium, a tranquilizer almost 10 times more potent than Librium. Currently, there are 8 benzodiazepines in clinical use as tranquilizers in the United States and some 15 others abroad. Rohypnol is one of the so-called date-rape drugs.

diazepam
Valium® (1963)

flunitrazepam
Rohypnol® (1963)

alprazolam
Xanax® (1970)

flurazepam
Dalmane® (1970)

clonazepam
Klonopin® (1975)

lorazepam
Ativan® (1977)

Viagra is a recent example of a drug that was discovered accidentally. Viagra was in clinical trials as a drug for heart ailments. The clinical trials were canceled when Viagra was found to be ineffective as a heart drug. However, those enrolled in the trials refused to return the remaining tablets. The pharmaceutical company then realized that the drug had other marketable effects.

12.9 THE REACTIONS OF ALDEHYDES AND KETONES WITH ALCOHOLS

The product formed when one equivalent of an alcohol adds to an *aldehyde* or a *ketone* is called a **hemiacetal.** The product formed when a second equivalent of alcohol is added is called an **acetal** (ass-ett-AL). An alcohol is a poor nucleophile, so an acid catalyst is required for the reaction to take place at a reasonable rate.

$$\underset{\text{an aldehyde or a ketone}}{R-\overset{O}{\overset{\|}{C}}-H(R)} + CH_3OH \underset{}{\overset{HCl}{\rightleftharpoons}} \underset{\text{a hemiacetal}}{R-\overset{OH}{\overset{|}{\underset{\underset{OCH_3}{|}}{C}}}-H(R)} \overset{CH_3OH,\ HCl}{\rightleftharpoons} \underset{\text{an acetal}}{R-\overset{OCH_3}{\overset{|}{\underset{\underset{OCH_3}{|}}{C}}}-H(R)} + H_2O$$

Hemi is the Greek word for "half." When one equivalent of alcohol has added to an aldehyde or a ketone, the hemiacetal that is formed is halfway to the final acetal, which contains groups from two equivalents of alcohol.

The mechanism for acetal formation shows that is it an addition-elimination reaction followed by a second addition.

MECHANISM FOR ACID-CATALYZED ACETAL FORMATION

the acid protonates the carbonyl oxygen

the nucleophile adds to the carbonyl carbon

$+ \ CH_3\ddot{O}H$

a hemiacetal

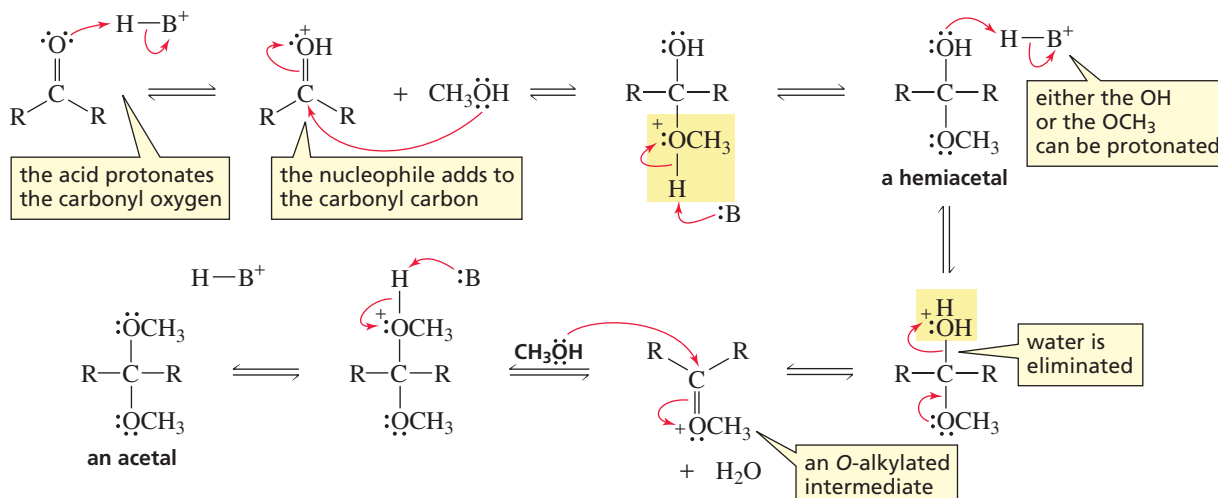
either the OH or the OCH_3 can be protonated

water is eliminated

an *O*-alkylated intermediate

$+ \ H_2O$

$CH_3\ddot{O}H$

an acetal

Notice that the pattern of three tetrahedral intermediates occurs again in this mechanism—namely,

protonated tetrahedral intermediate ⇌ neutral tetrahedral intermediate ⇌ protonated tetrahedral intermediate.

- The acid protonates the carbonyl oxygen, making the carbonyl carbon more susceptible to nucleophilic addition (Figure 12.2).
- The alcohol adds to the carbonyl carbon.
- Loss of a proton from the protonated tetrahedral intermediate forms the neutral tetrahedral intermediate (the hemiacetal).
- The hemiacetal is in equilibrium with its protonated form. The two oxygen atoms of the hemiacetal are equally basic, so either one can be protonated.
- Because the hemiacetal is unstable (the tetrahedral carbon is attached to two oxygens), water is eliminated from the second protonated intermediate, thereby forming an intermediate that is very reactive because of its positively charged oxygen.
- Nucleophilic addition to this intermediate by a second molecule of alcohol, followed by loss of a proton, forms the acetal.

Although the sp^3 carbon of an acetal is bonded to two oxygens, which suggests that it is not stable, the acetal can be isolated if the water that is eliminated is removed from the reaction mixture. If water is not available, the only compound the acetal can form is the *O*-alkylated intermediate, which is even less stable than the acetal.

$CH_3CH{=}O$

$CH_3CH{=}\overset{+}{O}H$

▲ **Figure 12.2**
The electrostatic potential maps show that the carbonyl carbon of the protonated aldehyde is more electrophilic (the blue is more intense) than the carbonyl carbon of the unprotonated aldehyde.

PROBLEM 23♦

Which of the following are

a. hemiacetals? **b.** acetals?

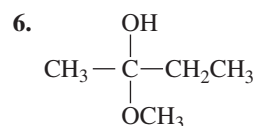
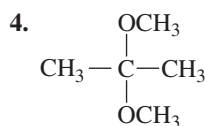
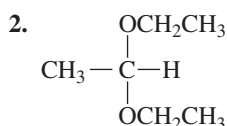
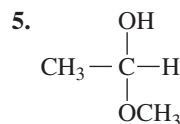
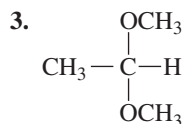
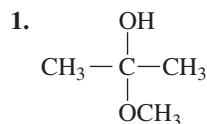
1. $CH_3C(OH)(OCH_3)CH_3$

2. $CH_3CH(OCH_2CH_3)_2$

3. $CH_3CH(OCH_3)_2$

4. $CH_3C(OCH_3)_2CH_3$

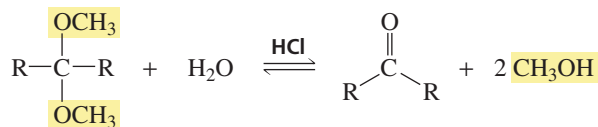
5. $CH_3CH(OH)(OCH_3)$

6. $CH_3C(OH)(OCH_3)CH_2CH_3$

PROBLEM 24

What are the products of the following reactions?

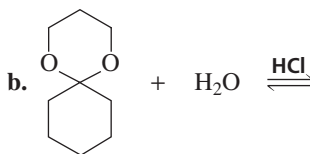
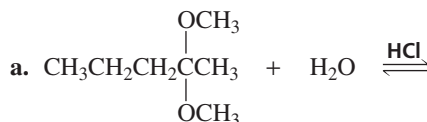
a. 3-pentanone + excess CH_3OH + HCl **b.** butanal + excess CH_3CH_2OH + HCl

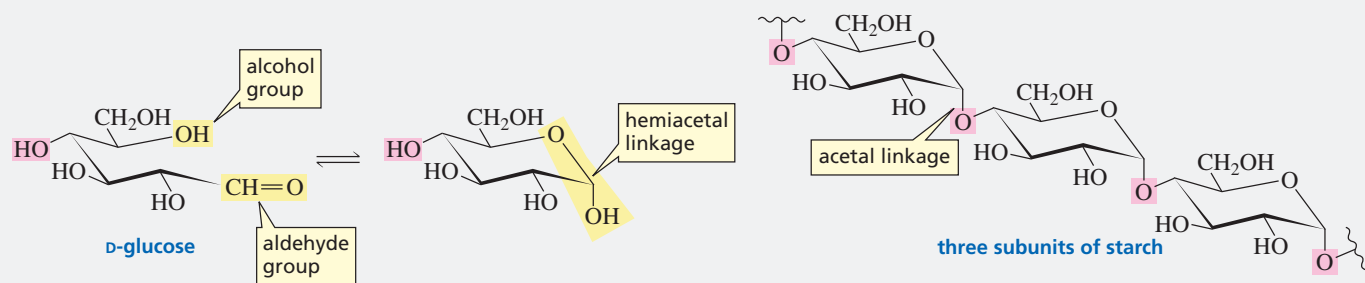
The acetal can be hydrolyzed back to the aldehyde or ketone in an acidic aqueous solution.

$$R{-}C(OCH_3)_2{-}R + H_2O \overset{HCl}{\rightleftharpoons} R{-}C({=}O){-}R + 2\,CH_3OH$$

PROBLEM 25

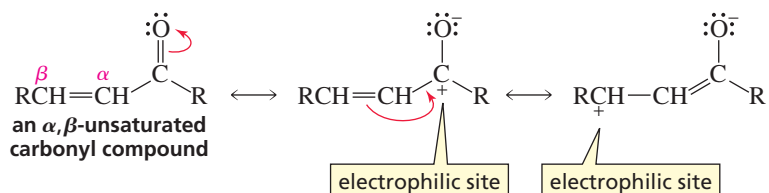
What are the products of the following reactions?

a. $CH_3CH_2CH_2C(OCH_3)_2CH_3 + H_2O \overset{HCl}{\rightleftharpoons}$

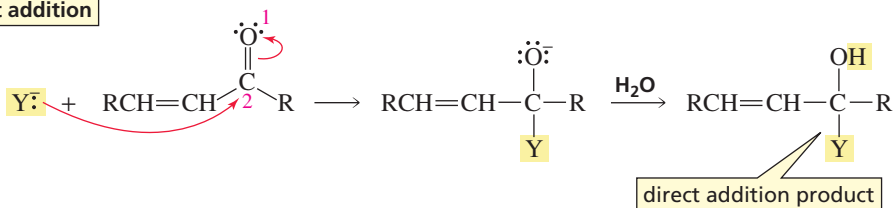
b. (spiro acetal of cyclohexanone and 1,3-propanediol) $+ H_2O \overset{HCl}{\rightleftharpoons}$

Carbohydrates Form Hemiacetals and Acetals

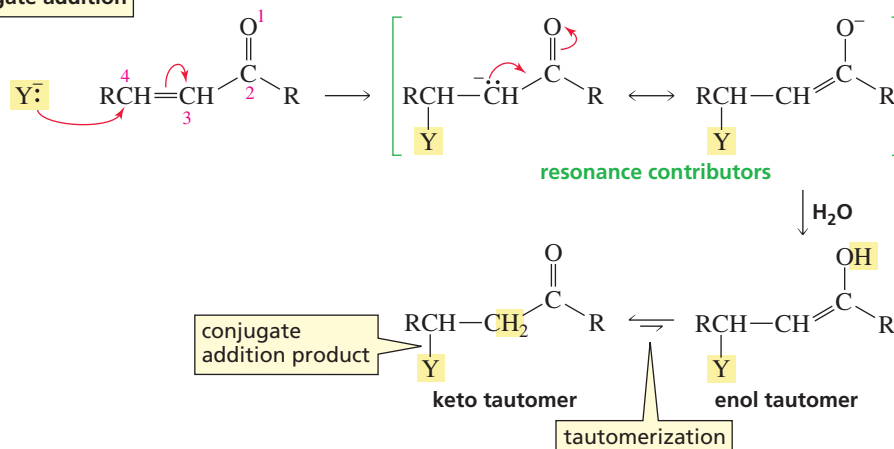
When you study carbohydrates in Chapter 16, you will see that the individual sugar units in a carbohydrate are held together by acetal groups. For example, the reaction of the aldehyde group and an alcohol group of D-glucose forms a cyclic compound that is a hemiacetal. Molecules of the cyclic compound are then hooked together by the reaction of the hemiacetal group of one molecule with an OH group of another, resulting in the formation of an acetal. Hundreds of cyclic glucose molecules hooked together by acetal groups are a major component of both starch and cellulose (Section 16.10).

12.10 NUCLEOPHILIC ADDITION TO α,β-UNSATURATED ALDEHYDES AND KETONES

The resonance contributors for an α,β-unsaturated carbonyl compound show that the molecule has two electrophilic sites: the carbonyl carbon and the β-carbon.

$$RCH{=}CH{-}C({=}O){-}R \longleftrightarrow RCH{=}CH{-}\overset{+}{C}(O^-){-}R \longleftrightarrow R\overset{+}{C}H{-}CH{=}C(O^-){-}R$$

This means that a nucleophile can add either to the carbonyl carbon or to the β-carbon. Nucleophilic addition to the carbonyl carbon is called **direct addition** or 1,2-addition.

direct addition

$$Y^- + RCH{=}CH{-}C({=}O){-}R \longrightarrow RCH{=}CH{-}C(O^-)(Y){-}R \xrightarrow{H_2O} RCH{=}CH{-}C(OH)(Y){-}R$$

Nucleophilic addition to the β-carbon is called **conjugate addition** or 1,4-addition, because it occurs at the 1- and 4-positions. The initial product of 1,4-addition is an enol, which tautomerizes to a ketone or to an aldehyde (Section 6.14). Thus, the overall reaction is addition to the carbon–carbon double bond, with the nucleophile adding to the β-carbon and a proton adding to the α-carbon.

conjugate addition

$$\text{Y:}^- + \overset{4}{\text{R}}\text{CH}{=}\overset{3}{\text{CH}}-\overset{2}{\text{C}}(=\overset{1}{\text{O}})-\text{R} \longrightarrow \left[\text{RCH(Y)}-\ddot{\text{C}}\text{H}^--\text{C}(=\text{O})-\text{R} \longleftrightarrow \text{RCH(Y)}-\text{CH}{=}\text{C}(\text{O}^-)-\text{R}\right]$$

resonance contributors

$\downarrow H_2O$

$$\underset{\text{keto tautomer}}{\text{RCH(Y)}-\text{CH}_2-\text{C}(=\text{O})-\text{R}} \rightleftharpoons \underset{\text{enol tautomer}}{\text{RCH(Y)}-\text{CH}{=}\text{C}(\text{OH})-\text{R}}$$

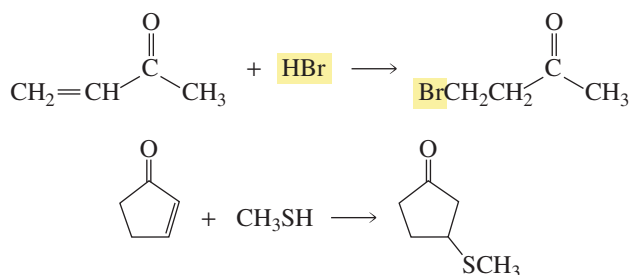
conjugate addition product

tautomerization

Nucleophiles that are *weak bases* form conjugate addition products.

Nucleophiles that are weak bases form conjugate addition products.

$$CH_2{=}CH-C(=O)-CH_3 + HBr \longrightarrow BrCH_2CH_2-C(=O)-CH_3$$

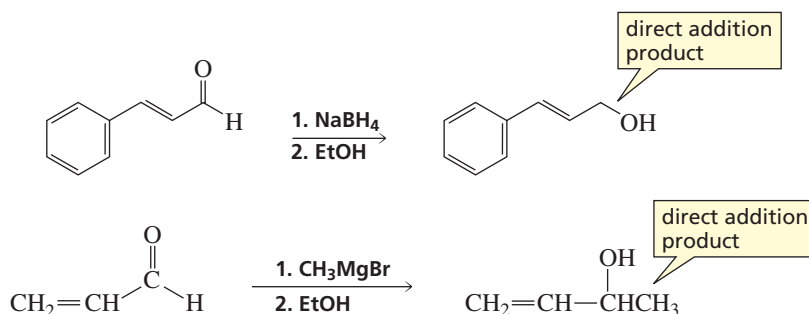
$$\text{2-cyclopentenone} + CH_3SH \longrightarrow \text{3-(methylthio)cyclopentanone } (SCH_3)$$

In general, nucleophiles that are *strong bases*, such as a Grignard reagent or a hydride ion, form direct addition products. (In the following reactions, ethanol protonates the alkoxide ion.)

Nucleophiles that are strong bases generally form direct addition products.

$$C_6H_5CH{=}CH-C(=O)H \xrightarrow[\text{2. EtOH}]{\text{1. NaBH}_4} C_6H_5CH{=}CH-CH_2OH$$

direct addition product

$$CH_2{=}CH-C(=O)-H \xrightarrow[\text{2. EtOH}]{\text{1. CH}_3\text{MgBr}} CH_2{=}CH-CH(OH)CH_3$$

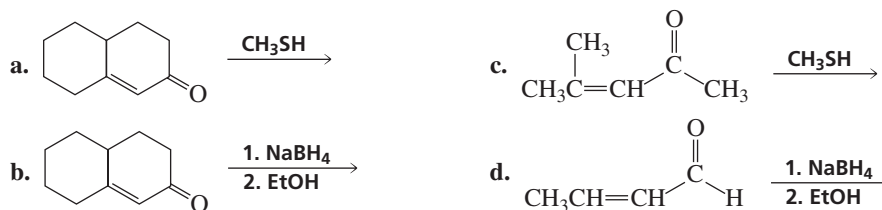
direct addition product

PROBLEM 26

What is the major product of each of the following reactions?

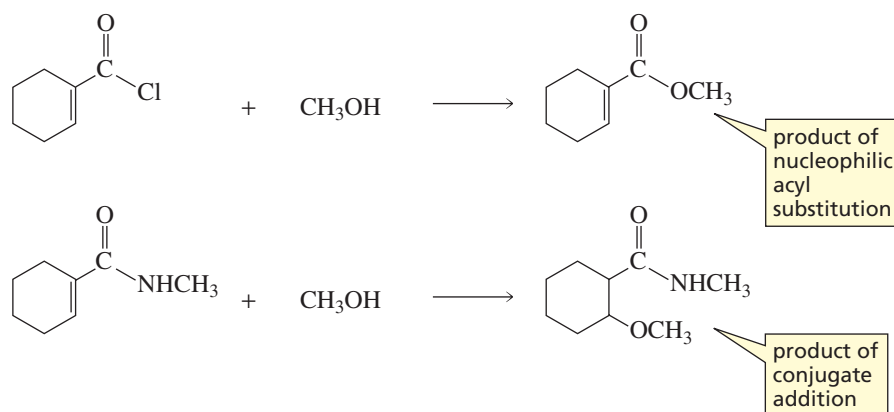
a. (bicyclic enone) $\xrightarrow{CH_3SH}$

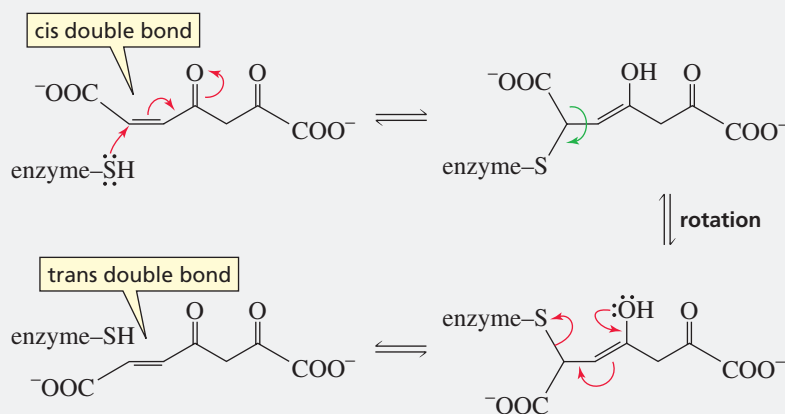
b. (bicyclic enone) $\xrightarrow[\text{2. EtOH}]{\text{1. NaBH}_4}$

c. $CH_3C(CH_3){=}CH-C(=O)-CH_3 \xrightarrow{CH_3SH}$

d. $CH_3CH{=}CH-C(=O)-H \xrightarrow[\text{2. EtOH}]{\text{1. NaBH}_4}$

12.11 NUCLEOPHILIC ADDITION TO α,β-UNSATURATED CARBOXYLIC ACID DERIVATIVES

α,β-Unsaturated carboxylic acid derivatives, like α,β-unsaturated aldehydes and ketones, have two electrophilic sites for nucleophilic addition. They can undergo *conjugate addition* or *nucleophilic acyl substitution*. Notice that α,β-unsaturated carboxylic acid derivatives undergo *nucleophilic acyl substitution* rather than *direct nucleophilic addition*, because they have a group that can be replaced by a nucleophile (Section 12.3).

Nucleophiles react with α,β-unsaturated carboxylic acid derivatives *with reactive carbonyl groups*, such as acyl chlorides, at the carbonyl group, forming nucleophilic acyl substitution products. Conjugate addition products are formed from the reaction of nucleophiles *with less reactive carbonyl groups*, such as esters and amides.

Enzyme-Catalyzed Cis–Trans Interconversion

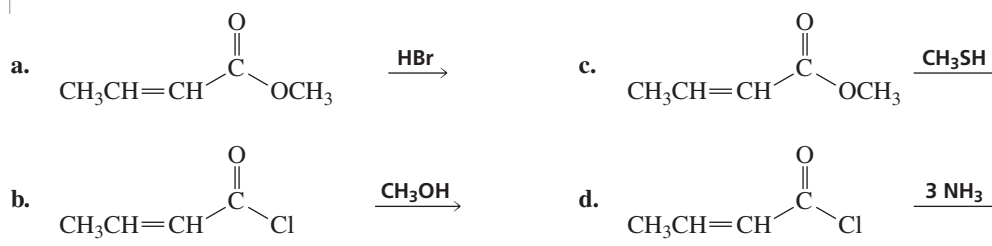
Enzymes that catalyze the interconversion of cis and trans isomers are called cis–trans isomerases. These isomerases are all known to contain thiol (SH) groups. Thiols are weak bases and, therefore, add to the β-carbon of an α,β-unsaturated ketone (conjugate addition), forming a carbon—carbon single bond that rotates before the enol is able to tautomerize to the ketone. When tautomerization occurs, the absence of a proton at the active site of the enzyme in the vicinity of the α-carbon prevents the addition of a proton to the α-carbon. Therefore, the thiol is eliminated, leaving the compound as it was originally except for the configuration of the double bond.

PROBLEM 27

What is the major product of each of the following reactions?

a. $CH_3CH{=}CH{-}C({=}O){-}OCH_3 \xrightarrow{\text{HBr}}$

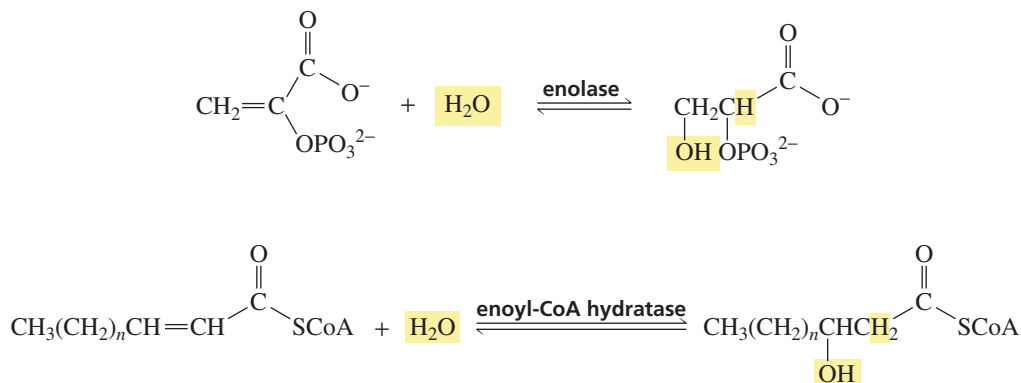
b. $CH_3CH{=}CH{-}C({=}O){-}Cl \xrightarrow{CH_3OH}$

c. $CH_3CH{=}CH{-}C({=}O){-}OCH_3 \xrightarrow{CH_3SH}$

d. $CH_3CH{=}CH{-}C({=}O){-}Cl \xrightarrow{3\ NH_3}$

12.12 CONJUGATE ADDITION REACTIONS IN BIOLOGICAL SYSTEMS

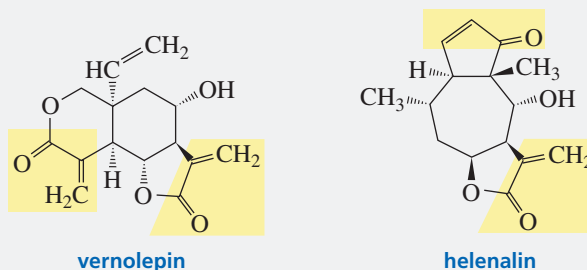
Several reactions in biological systems involve the conjugate addition to α,β-unsaturated carbonyl compounds. Below are examples of two of them. The first occurs in gluconeogenesis—the synthesis of glucose from pyruvate (Section 19.11). The second occurs in the oxidation of fatty acids (Section 19.4).

$$CH_2{=}C(OPO_3^{2-}){-}C({=}O){-}O^- + H_2O \underset{}{\overset{\text{enolase}}{\rightleftharpoons}} CH_2(OH){-}CH(OPO_3^{2-}){-}C({=}O){-}O^-$$

$$CH_3(CH_2)_nCH{=}CH{-}C({=}O){-}SCoA + H_2O \overset{\text{enoyl-CoA hydratase}}{\rightleftharpoons} CH_3(CH_2)_nCH(OH)CH_2{-}C({=}O){-}SCoA$$

Cancer Chemotherapy

Two compounds—vernolepin and helenalin—owe their effectiveness as anticancer drugs to conjugate addition reactions.

vernolepin

helenalin

Cancer cells are cells that have lost the ability to control their growth, so they proliferate rapidly. DNA polymerase is an enzyme that a cell needs in order to make a copy of its DNA for a new cell. DNA polymerase has an SH group at its active site. Each of these drugs has two α,β-unsaturated carbonyl groups. When an SH group of DNA polymerase adds to the β-carbon of one of the α,β-unsaturated carbonyl groups of vernolepin or helenalin, the enzyme is inactivated because the active site of the enzyme is now blocked by the drug, so the enzyme cannot bind its substrate (see page 198).

active
enzyme
HS
$=CH_2$
O
O
conjugate addition
inactive
enzyme
S
CH_2
O
O

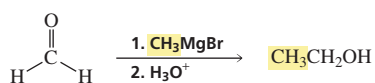
SOME IMPORTANT THINGS TO REMEMBER

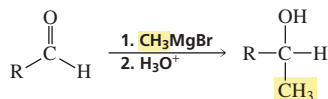
- **Aldehydes** and **ketones** have an acyl group attached to an H and an R, respectively.
- Aldehydes and ketones undergo **nucleophilic addition reactions** with strongly basic (R^- and H^-) nucleophiles, and undergo **nucleophilic addition–elimination reactions** with O and N nucleophiles.
- Acyl chlorides and esters undergo a nucleophilic acyl substitution reaction with strongly basic nucleophiles (R^- and H^-) to form a ketone or an aldehyde, which then undergoes a nucleophilic addition reaction with a second equivalent of the nucleophile.
- Electronic and steric factors cause an aldehyde to be more reactive than a ketone toward nucleophilic addition.
- Aldehydes and ketones are less reactive than acyl halides and acid anhydrides, and are more reactive than esters, carboxylic acids, and amides.
- Grignard reagents react with formaldehyde to form a primary alcohol, with aldehydes to form secondary alcohols, with ketones, esters, and acyl halides to form tertiary alcohols, and with carbon dioxide to form carboxylic acids.
- An aldehyde or a ketone reacts with hydrogen cyanide to form a cyanohydrin.
- Aldehydes, acyl chlorides, esters, and carboxylic acids are reduced by hydride ion to primary alcohols; ketones are reduced to secondary alcohols; and amides are reduced to amines.
- Aldehydes and ketones react with primary amines to form **imines.**
- Imines are hydrolyzed under acidic conditions back to the carbonyl compound and the protonated primary amine.
- Reductive amination is the reduction of an imine to an amine.
- Acid-catalyzed addition of an alcohol to an aldehyde or a ketone forms a **hemiacetal;** a second addition of alcohol forms an **acetal.** Acetal formation is reversible.
- Nucleophilic addition to the carbonyl carbon of an α,β-unsaturated aldehyde or ketone is called **direct addition;** addition to the β-carbon is called **conjugate addition.**
- Nucleophiles that are weak bases—namely, halide ions, water, alcohols, and amines—form conjugate addition products.
- Nucleophiles that are strong bases—namely, hydride ion and Grignard reagents—generally form direct addition products.
- Nucleophiles form nucleophilic acyl substitution products with reactive α,β-unsaturated carboxylic acid derivatives and form conjugate addition products with less reactive α,β-unsaturated carboxylic acid derivatives.

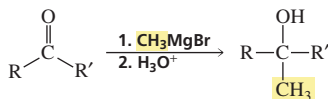
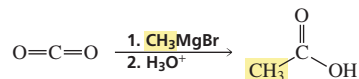
SUMMARY OF REACTIONS

1. Reactions of *carbonyl compounds* with Grignard reagents (Section 12.5)

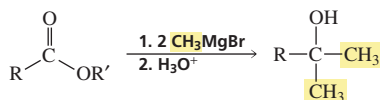
a. Reaction of *formaldehyde* with a Grignard reagent forms a primary alcohol. The mechanism is shown on page 465.

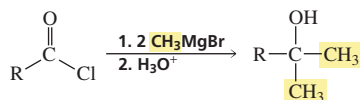
$$HCHO \xrightarrow[\text{2. } H_3O^+]{\text{1. } CH_3MgBr} CH_3CH_2OH$$

b. Reaction of an *aldehyde* (other than formaldehyde) with a Grignard reagent forms a secondary alcohol. The mechanism is shown on page 465.

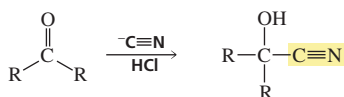
$$RCHO \xrightarrow[\text{2. } H_3O^+]{\text{1. } CH_3MgBr} R{-}CH(OH){-}CH_3$$

c. Reaction of a *ketone* with a Grignard reagent forms a tertiary alcohol. The mechanism is shown on page 465.

$$RCOR' \xrightarrow[\text{2. } H_3O^+]{\text{1. } CH_3MgBr} R{-}C(OH)(CH_3){-}R'$$

d. Reaction of CO_2 with a Grignard reagent forms a carboxylic acid. The mechanism is shown on page 466.

$$O{=}C{=}O \xrightarrow[\text{2. } H_3O^+]{\text{1. } CH_3MgBr} CH_3COOH$$

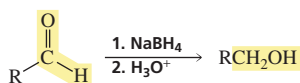
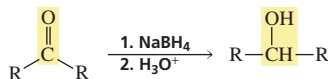
e. Reaction of an *ester* with excess Grignard reagent forms a tertiary alcohol with two identical subunits. The mechanism is shown on page 467.

$$RCOOR' \xrightarrow[\text{2. } H_3O^+]{\text{1. 2 } CH_3MgBr} R{-}C(OH)(CH_3){-}CH_3$$

f. Reaction of an *acyl chloride* with excess Grignard reagent forms a tertiary alcohol with two identical substituents.

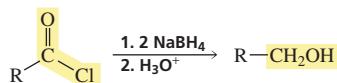
$$RCOCl \xrightarrow[\text{2. } H_3O^+]{\text{1. 2 } CH_3MgBr} R{-}C(OH)(CH_3){-}CH_3$$

2. Reaction of an *aldehyde* or a *ketone* with cyanide ion under acidic conditions forms a cyanohydrin (Section 12.6). The mechanism is shown on page 469.

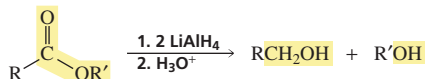
$$RCOR \xrightarrow[HCl]{^{-}C{\equiv}N} R{-}C(OH)(R){-}C{\equiv}N$$

3. Reactions of *carbonyl compounds* with hydride ion donors (Section 12.7)

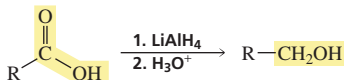
a. Reaction of an *aldehyde* with sodium borohydride forms a primary alcohol. The mechanism is shown on page 471.

$$RCHO \xrightarrow[\text{2. } H_3O^+]{\text{1. } NaBH_4} RCH_2OH$$

b. Reaction of a *ketone* with sodium borohydride forms a secondary alcohol. The mechanism is shown on page 471.

$$RCOR \xrightarrow[\text{2. } H_3O^+]{\text{1. } NaBH_4} R{-}CH(OH){-}R$$

c. Reaction of an *acyl chloride* with sodium borohydride forms a primary alcohol. The mechanism is shown on page 471.

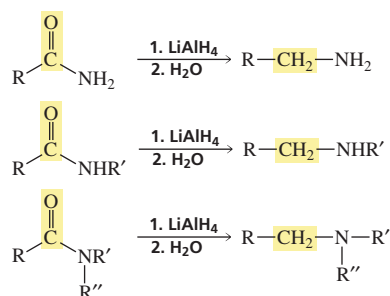
$$RCOCl \xrightarrow[\text{2. } H_3O^+]{\text{1. 2 } NaBH_4} R{-}CH_2OH$$

d. Reaction of an *ester* with lithium aluminum hydride forms a primary alcohol and the alcohol that corresponds to the leaving group. The mechanism is shown on page 472.

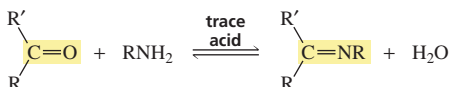
$$RCOOR' \xrightarrow[\text{2. } H_3O^+]{\text{1. 2 } LiAlH_4} RCH_2OH + R'OH$$

e. Reaction of a *carboxylic acid* with lithium aluminum hydride forms a primary alcohol.

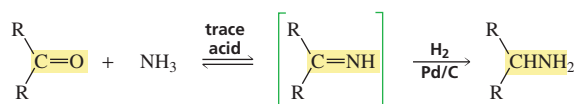
$$RCOOH \xrightarrow[\text{2. } H_3O^+]{\text{1. } LiAlH_4} R{-}CH_2OH$$

f. Reaction of an *amide* with lithium aluminum hydride forms an amine.

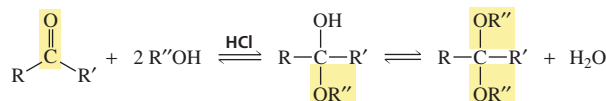
$$\text{RC(=O)NH}_2 \xrightarrow[\text{2. H}_2\text{O}]{\text{1. LiAlH}_4} \text{R—CH}_2\text{—NH}_2$$

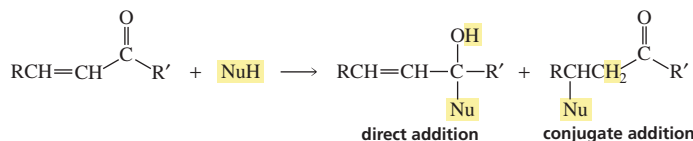
$$\text{RC(=O)NHR}' \xrightarrow[\text{2. H}_2\text{O}]{\text{1. LiAlH}_4} \text{R—CH}_2\text{—NHR}'$$

$$\text{RC(=O)NR}'\text{R}'' \xrightarrow[\text{2. H}_2\text{O}]{\text{1. LiAlH}_4} \text{R—CH}_2\text{—N(R}'')\text{—R}'$$

4. Reaction of an *aldehyde* or a *ketone* with a *primary amine* forms an imine (Section 12.8). The mechanism is shown on page 474.

$$\text{R}'\text{(R)C=O} + \text{RNH}_2 \overset{\text{trace acid}}{\rightleftharpoons} \text{R}'\text{(R)C=NR} + \text{H}_2\text{O}$$

5. *Reductive amination:* the imine formed from the reaction of an aldehyde or a ketone with ammonia can be reduced to a primary amine (Section 12.8).

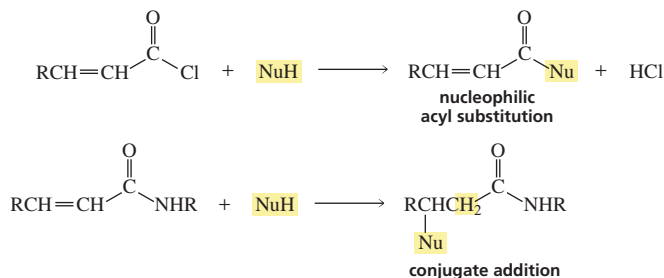
$$\text{R(R)C=O} + \text{NH}_3 \overset{\text{trace acid}}{\rightleftharpoons} \left[\text{R(R)C=NH}\right] \xrightarrow[\text{Pd/C}]{\text{H}_2} \text{R(R)CHNH}_2$$

6. Reaction of an *aldehyde* or a *ketone* with excess alcohol first forms a hemiacetal and then an acetal (Section 12.9). The mechanism is shown on page 478.

$$\text{RC(=O)R}' + 2\,\text{R}''\text{OH} \overset{\text{HCl}}{\rightleftharpoons} \text{R—C(OH)(OR}'')\text{—R}' \rightleftharpoons \text{R—C(OR}'')(\text{OR}'')\text{—R}' + \text{H}_2\text{O}$$

7. Reaction of an *α,β-unsaturated aldehyde* or a *ketone* with a nucleophile forms a direct addition product or a conjugate addition product, depending on the nucleophile (Section 12.10). The mechanism is shown on pages 479–482.

$$\text{RCH=CHC(=O)R}' + \text{NuH} \longrightarrow \underset{\text{direct addition}}{\text{RCH=CH—C(OH)(Nu)—R}'} + \underset{\text{conjugate addition}}{\text{RCH(Nu)CH}_2\text{C(=O)R}'}$$

Nucleophiles that are weak bases (CH_3OH, H_2O, RSH, RNH_2, Br^-) form conjugate addition products. Nucleophiles that are strong bases (RMgBr, H^-) generally form direct addition products.

8. Reaction of an *α,β-unsaturated carboxylic acid derivative* with a nucleophile forms a nucleophilic acyl substitution product with a reactive carbonyl group and a conjugate addition product with a less reactive carbonyl group (Section 12.11).

$$\text{RCH=CHC(=O)Cl} + \text{NuH} \longrightarrow \underset{\text{nucleophilic acyl substitution}}{\text{RCH=CHC(=O)Nu}} + \text{HCl}$$

$$\text{RCH=CHC(=O)NHR} + \text{NuH} \longrightarrow \underset{\text{conjugate addition}}{\text{RCH(Nu)CH}_2\text{C(=O)NHR}}$$

PROBLEMS

28. Draw the structure for each of the following:

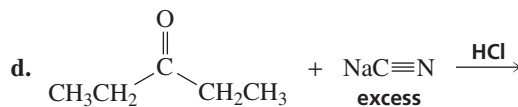
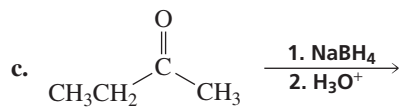
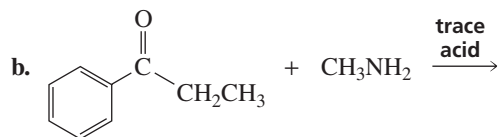
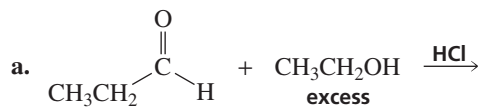
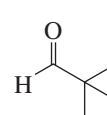
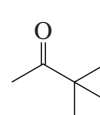
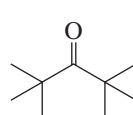
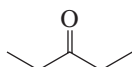
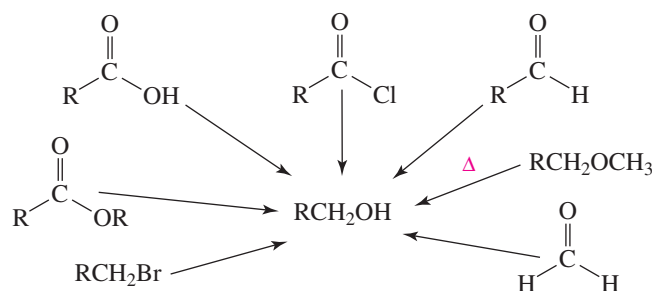
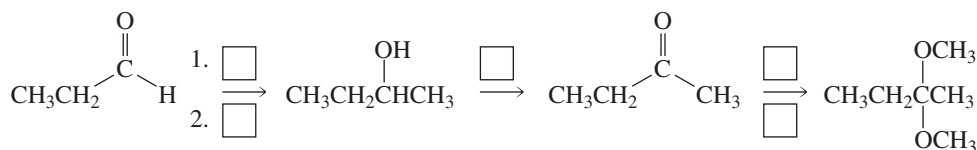
a. isobutyraldehyde
b. diisopentyl ketone
c. 3-methylcyclohexanone
d. 2,4-pentanedione
e 4-bromo-3-heptanone
f. 4-bromohexanal

29. What are the products of the following reactions?

a. $CH_3CH_2C(=O)H + CH_3CH_2OH$ (excess) $\xrightarrow{HCl}$

b. $C_6H_5C(=O)CH_2CH_3 + CH_3NH_2$ $\xrightarrow{\text{trace acid}}$

c. $CH_3CH_2C(=O)CH_3$ $\xrightarrow{\text{1. NaBH}_4 \text{ 2. H}_3\text{O}^+}$

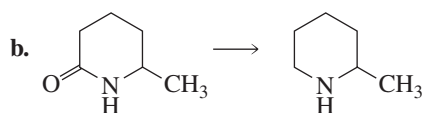
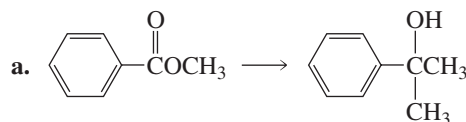
d. $CH_3CH_2C(=O)CH_2CH_3 + NaC{\equiv}N$ (excess) $\xrightarrow{HCl}$

30. List the following compounds in order from most reactive to least reactive toward nucleophilic addition:

31. Show the reagents required to form the primary alcohol in each of the following reactions:

$RC(=O)OH$, $RC(=O)Cl$, $RC(=O)H$, RCH_2OCH_3 (Δ), $RC(=O)OR$, RCH_2Br, $HC(=O)H$ → RCH_2OH

32. Fill in the boxes:

$CH_3CH_2C(=O)H$ $\xrightarrow{1. \square \; 2. \square}$ $CH_3CH_2CH(OH)CH_3$ $\xrightarrow{\square}$ $CH_3CH_2C(=O)CH_3$ $\xrightarrow{\square \; \square}$ $CH_3CH_2C(OCH_3)_2CH_3$

33. Indicate how the following compounds could be prepared from the given starting materials:

a. $C_6H_5C(=O)OCH_3 \longrightarrow C_6H_5C(OH)(CH_3)CH_3$

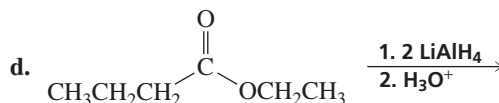
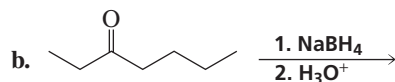
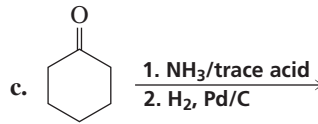
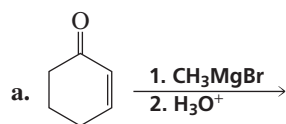
b. 6-methyl-2-piperidinone $\longrightarrow$ 2-methylpiperidine

34. What class of alcohol (primary, secondary, or tertiary) is formed from the reaction of ethyl benzoate with excess Grignard reagent followed by the addition of dilute acid?

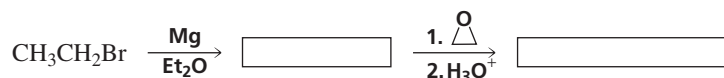
35. What are the products of the following reactions? Show all stereoisomers that are formed.

a. 2-cyclohexenone $\xrightarrow{\text{1. CH}_3\text{MgBr} \text{ 2. H}_3\text{O}^+}$

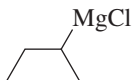
b. 2-heptanone $\xrightarrow{\text{1. NaBH}_4 \text{ 2. H}_3\text{O}^+}$

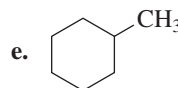
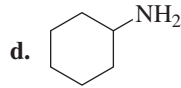
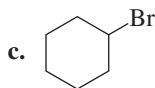
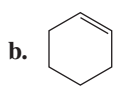
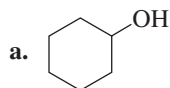
c. cyclohexanone $\xrightarrow{\text{1. NH}_3\text{/trace acid} \text{ 2. H}_2\text{, Pd/C}}$

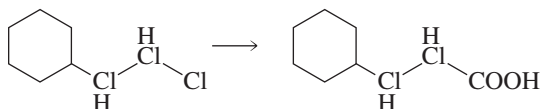
d. $CH_3CH_2CH_2C(=O)OCH_2CH_3$ $\xrightarrow{\text{1. 2 LiAlH}_4 \text{ 2. H}_3\text{O}^+}$

36. Put the appropriate compound in each box:

CH_3CH_2Br $\xrightarrow{\text{Mg, Et}_2\text{O}}$ $\square$ $\xrightarrow{\text{1. ethylene oxide} \text{ 2. H}_3\text{O}^+}$ $\square$

37. Write the mechanism for the acid-catalyzed hydrolysis of an imine to a carbonyl compound and a protonated primary amine.

38. What alcohol would be formed from the reaction of the following Grignard reagent with ethylene oxide followed by the addition of acid?

MgCl

39. Using cyclohexanone as the starting material, describe how each of the following compounds could be synthesized:

a. OH **b.** **c.** Br **d.** NH_2 **e.** CH_3

40. Show two ways the following compound could be prepared from the given starting material:

H Cl Cl H Cl → H Cl Cl H COOH

41. Fill in the boxes with the appropriate reagents:

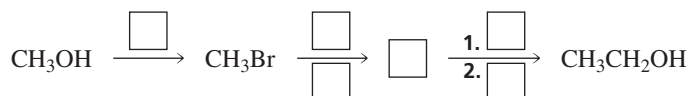
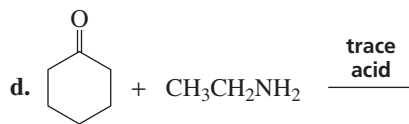
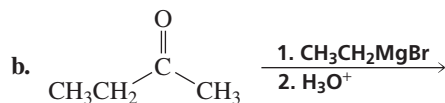
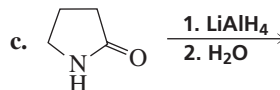
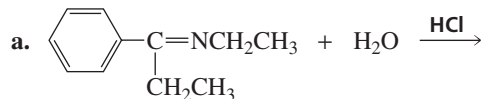
$CH_3OH \xrightarrow{\square} CH_3Br \xrightarrow[\square]{\square} \square \xrightarrow[2.\ \square]{1.\ \square} CH_3CH_2OH$

42. What are the products of the following reactions?

a. $C_6H_5C(CH_2CH_3){=}NCH_2CH_3 + H_2O \xrightarrow{HCl}$

b. $CH_3CH_2C(=O)CH_3 \xrightarrow[2.\ H_3O^+]{1.\ CH_3CH_2MgBr}$

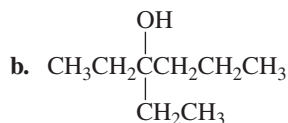
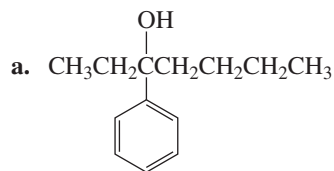
c. (N-H lactam, =O) $\xrightarrow[2.\ H_2O]{1.\ LiAlH_4}$

d. (cyclohexanone) $+ CH_3CH_2NH_2 \xrightarrow{\text{trace acid}}$

43. How could you convert *N*-methylbutanamide into the following compounds?

a. butylmethylamine **b.** butanoic acid **c.** methyl butanoate **d.** butyl alcohol

44. List three different sets of reagents (each set consisting of a carbonyl compound and a Grignard reagent) that could be used to prepare each of the following tertiary alcohols:

a. $CH_3CH_2C(OH)(C_6H_5)CH_2CH_2CH_2CH_3$

b. $CH_3CH_2C(OH)(CH_2CH_3)CH_2CH_2CH_3$

45. What product is formed when 2-methyl-2-cycloheptenone reacts with each of the following reagents?

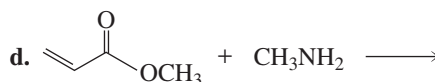
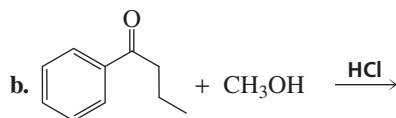
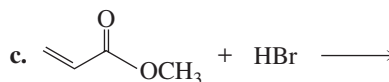
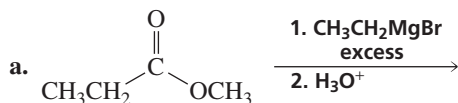
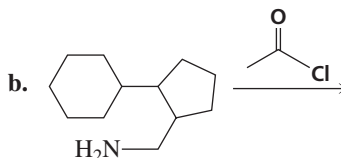
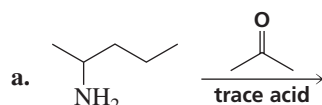
a. $CH_3CH_2CH_2MgBr$ followed by H_3O^+ **b.** CH_3SH **c.** HCl

46. What are the products of the following reactions?

a. $CH_3CH_2C(=O)OCH_3 \xrightarrow[2.\ H_3O^+]{1.\ CH_3CH_2MgBr\ \text{excess}}$

b. (phenyl ketone, O) $+ CH_3OH \xrightarrow{HCl}$

c. (O, OCH_3) $+ HBr \longrightarrow$

d. (O, OCH_3) $+ CH_3NH_2 \longrightarrow$

47. What is the organic product of each of the following reactions?

a. (NH_2) $\xrightarrow[\text{trace acid}]{O}$

b. (H_2N) $\xrightarrow{O,\ Cl}$

48. Propose a mechanism for the following reaction:

+ CH_3CH_2OH $\xrightarrow{HCl}$ O OCH_2CH_3

49. Propose a mechanism for the following reaction:

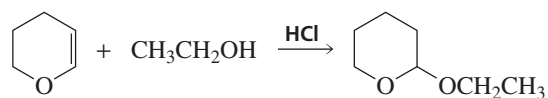
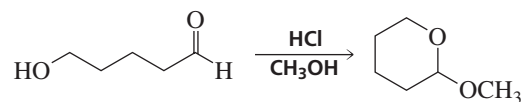
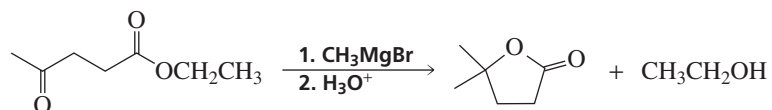
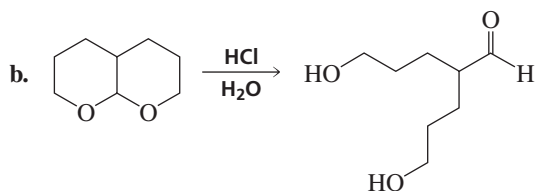
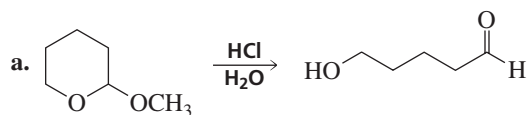
HO ... O H $\xrightarrow[CH_3OH]{HCl}$ O OCH_3

50. Propose a mechanism for the following reaction:

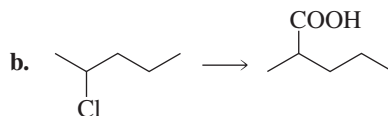
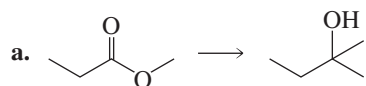
O O OCH_2CH_3 $\xrightarrow[2.\ H_3O^+]{1.\ CH_3MgBr}$ O O + CH_3CH_2OH

51. Propose a mechanism for each of the following reactions:

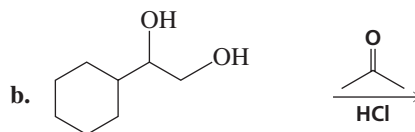
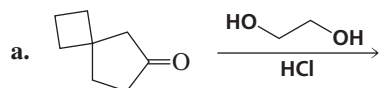
a. O OCH_3 $\xrightarrow[H_2O]{HCl}$ HO O H

b. O O $\xrightarrow[H_2O]{HCl}$ HO O H HO

52. Indicate how the following compounds could be prepared from the given starting materials:

a. O O ⟶ OH

b. Cl ⟶ COOH

53. What is the product of each of the following reactions?

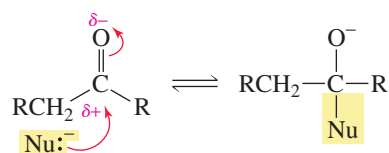
a. O $\xrightarrow[HCl]{HO\quad OH}$

b. OH OH $\xrightarrow[HCl]{O}$

13 Reactions at the α-Carbon of Carbonyl Compounds

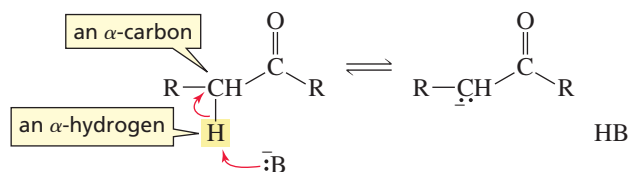
a paper mulberry tree

Fifteen aromatase inhibitors, compounds used in the treatment of breast cancer, have been isolated from the leaves of the paper mulberry tree (see page 500).

When we looked at the reactions of carbonyl compounds in Chapters 11 and 12, we saw that their site of reactivity is the partially positively charged carbonyl carbon to which a nucleophile adds.

$$\mathrm{RCH_2}\overset{\delta+}{\underset{}{\mathrm{C}}}(=\overset{\delta-}{\mathrm{O}})\mathrm{R} + \mathrm{Nu{:}^-} \rightleftharpoons \mathrm{RCH_2{-}C(O^-)(Nu){-}R}$$

Many carbonyl compounds have a second site of reactivity—namely, a hydrogen bonded to *a carbon that is adjacent to the carbonyl carbon*. This hydrogen is sufficiently acidic to be removed by a strong base. The carbon adjacent to a carbonyl carbon is called an ***α*-carbon;** a hydrogen bonded to an α-carbon is called an ***α*-hydrogen.**

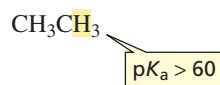
$$\mathrm{R{-}CH(H){-}C(=O){-}R} + {:}\mathrm{B^-} \rightleftharpoons \mathrm{R{-}\ddot{C}H^-{-}C(=O){-}R} + \mathrm{HB}$$

an α-carbon

an α-hydrogen

In Section 13.1, you will find out why a hydrogen bonded to an α-carbon is more acidic than hydrogens bonded to other sp^3 carbons, and then you will look at some reactions that result from this acidity. Later in the chapter, you will see that a hydrogen is not the only substituent that can be removed from an α-carbon: a carboxyl group bonded to an α-carbon can be removed as CO_2. At the end of the chapter, you will be introduced to some important biological reactions that rely on the ability to remove a *proton* or a *carboxyl* group from an α-carbon.

13.1 THE ACIDITY OF AN α-HYDROGEN

Hydrogen and carbon have similar electronegativities, which means that the two atoms share the electrons that bond them together almost equally. Consequently, a hydrogen bonded to a carbon is usually not acidic. This is particularly true for hydrogens bonded to sp^3 carbons because these carbons are the most similar to hydrogen in electronegativity. For example, the pK_a of ethane is greater than 60 (Section 2.6).

CH_3CH_3 — pK_a > 60

A hydrogen bonded to an sp^3 carbon that is adjacent to a carbonyl carbon, however, is much more acidic than hydrogens bonded to other sp^3 carbons. For example, the pK_a value for dissociation of a proton from the α-carbon of an aldehyde or a ketone ranges from 16 to 20, and the pK_a value for dissociation of a proton attached to the α-carbon of an ester is about 25 (Table 13.1). Notice that although an *α-hydrogen* is more acidic than most other carbon-bound hydrogens, it is less acidic than a hydrogen of water (pK_a = 15.7).

The α-hydrogen of a ketone or an aldehyde is more acidic than the α-hydrogen of an ester.

$RCH_2C(=O)H$ and $RCH_2C(=O)R$ — pK_a ~ 16–20

$RCH_2C(=O)OR$ — pK_a ~ 25

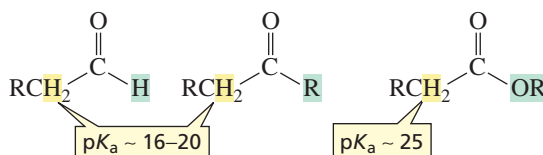



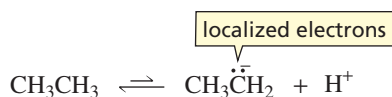
Table 13.1 The pK_a Values of Some Carbon Acids

	pK_a		pK_a
$H-CH_2C(=O)OCH_2CH_3$	25	$CH_3C(=O)CH(H)C(=O)OCH_2CH_3$	10.7
$H-CH_2C(=O)CH_3$	20	$CH_3C(=O)CH(H)C(=O)CH_3$	8.9
$H-CH_2C(=O)H$	17	$CH_3C(=O)CH(H)C(=O)H$	5.9

A hydrogen bonded to an α-carbon is more acidic than hydrogens bonded to other sp^3 carbons, because the base formed when a proton is removed from an α-carbon is relatively stable. And, as we have seen, the more stable the base, the stronger is its conjugate acid (Section 2.6).

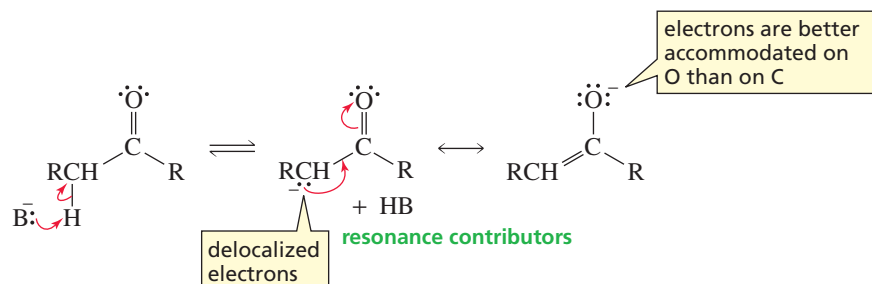
Why is the base formed by removing a proton from an α-carbon more stable than bases formed by removing a proton from other sp^3 carbons? When a proton is removed from ethane, the electrons left behind are localized—that is, they reside solely on a carbon. The carbanion is unstable because carbon is not very electronegative. As a result, the pK_a of its conjugate acid is very high.

localized electrons

$$CH_3CH_3 \rightleftharpoons CH_3\ddot{C}H_2^- + H^+$$

In contrast, when a proton is removed from an α-carbon, two factors combine to increase the stability of the base that is formed. First, the electrons left behind when the proton is removed are delocalized, and electron delocalization increases stability (Section 7.6). More importantly, the electrons are delocalized onto an oxygen, an atom that is better able to accommodate the electrons because it is more electronegative than carbon.

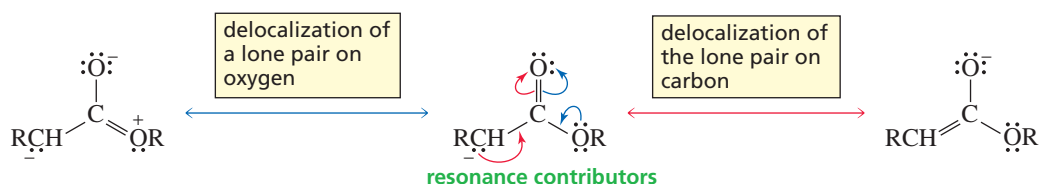
electrons are better accommodated on O than on C

delocalized electrons

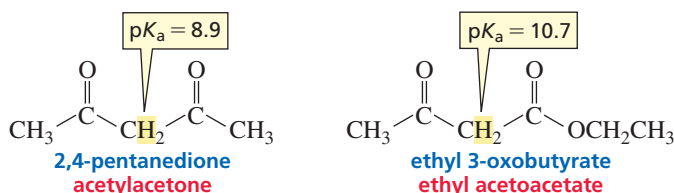
resonance contributors

Why are aldehydes and ketones (pK_a = 16–20) more acidic than esters (pK_a = 25)? The electrons left behind when a proton is removed from the α-carbon of an ester are not as readily delocalized onto the carbonyl oxygen (indicated by the red arrows) as they would be in an aldehyde or a ketone. This is because the oxygen of the OR group of the ester also has a lone pair that can be delocalized onto the carbonyl oxygen (indicated by the blue arrows). Thus, the pair of electrons from carbon and the pair of electrons from oxygen compete for delocalization onto the same oxygen.

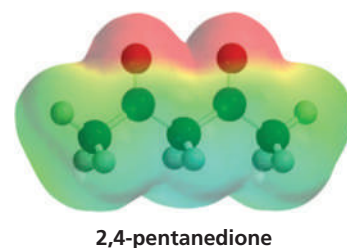
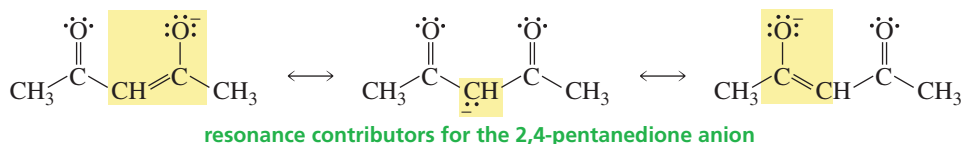
delocalization of a lone pair on oxygen

delocalization of the lone pair on carbon

resonance contributors

If the α-carbon is *between* two carbonyl groups, the acidity of its α-hydrogen is even greater (Table 13.1). For example, the pK_a value for dissociation of a proton from the α-carbon of 2,4-pentanedione, a compound with an α-carbon between two ketone carbonyl groups, is 8.9. And the pK_a value for dissociation of a proton from the α-carbon of ethyl 3-oxobutyrate, which is between a ketone carbonyl group and an ester carbonyl group, is 10.7.

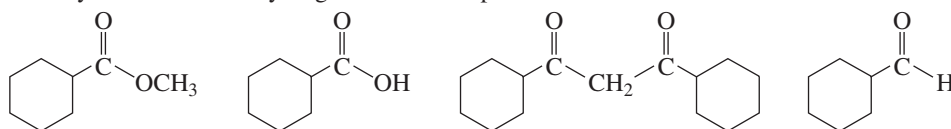
$pK_a = 8.9$ — **2,4-pentanedione** / **acetylacetone**

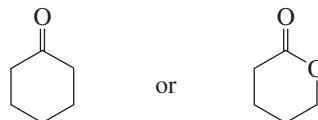
$pK_a = 10.7$ — **ethyl 3-oxobutyrate** / **ethyl acetoacetate**

The acidity of α-hydrogens bonded to carbons flanked by two carbonyl groups increases, because the electrons left behind when the proton is removed can be delocalized onto either of *two* oxygens.

resonance contributors for the 2,4-pentanedione anion

2,4-pentanedione

PROBLEM 1

Identify the most acidic hydrogen in each compound.

$C_6H_{11}C(=O)OCH_3$ $\quad$ $C_6H_{11}C(=O)OH$ $\quad$ $C_6H_{11}C(=O)CH_2C(=O)C_6H_{11}$ $\quad$ $C_6H_{11}C(=O)H$

PROBLEM 2♦

a. Which compound is a stronger acid? **b.** Which compound has a greater pK_a value?

PROBLEM 3♦

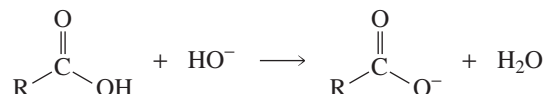
Why is 2,4-pentanedione a stronger acid than ethyl 3-oxobutyrate?

PROBLEM-SOLVING STRATEGY

The Acid–Base Behavior of a Carbonyl Compound

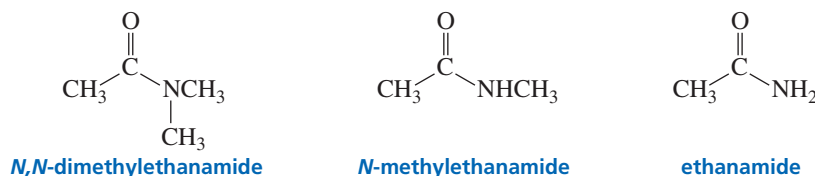
Explain why a base cannot remove a proton from the α-carbon of a carboxylic acid.

If a base cannot remove a proton from the α-carbon, then the base must react with another portion of the molecule more rapidly. Because the proton on the carboxyl group is more acidic (pK_a ~ 5) than the proton on the α-carbon, we can conclude that the base removes a proton from the carboxyl group rather than from the α-carbon.

$$RC(=O)OH + HO^- \longrightarrow RC(=O)O^- + H_2O$$

Now use the strategy you have just learned to solve Problem 4.

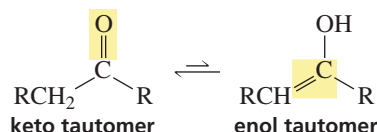
PROBLEM 4♦

Explain why a base can remove a proton from the α-carbon of *N,N*-dimethylethanamide but not from the α-carbon of either *N*-methylethanamide or ethanamide.

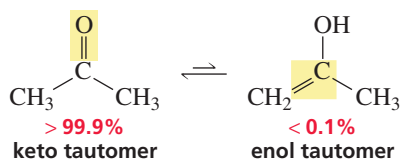
$CH_3C(=O)N(CH_3)_2$	$CH_3C(=O)NHCH_3$	$CH_3C(=O)NH_2$
***N,N*-dimethylethanamide**	***N*-methylethanamide**	**ethanamide**

PROBLEM 5♦

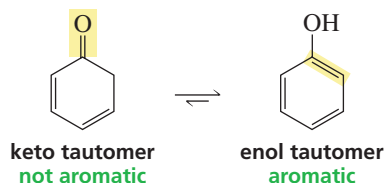
Explain why HO^- cannot remove a proton from the α-carbon of an acyl chloride.

13.2 KETO–ENOL TAUTOMERS

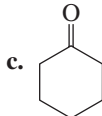
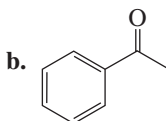
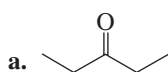
A ketone exists in equilibrium with its enol tautomer. Recall that **tautomers** are isomers that are in rapid equilibrium (Section 6.13). *Keto–enol tautomers differ in the location of a double bond and a hydrogen.*

For most ketones, the **enol tautomer** is much less stable than the **keto tautomer.** For example, an aqueous solution of acetone exists as an equilibrium mixture of more than 99.9% keto tautomer and less than 0.1% enol tautomer.

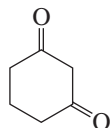
$$CH_3COCH_3 \rightleftharpoons CH_2{=}C(OH)CH_3$$

> 99.9% keto tautomer; < 0.1% enol tautomer

Phenol is unusual in that its enol tautomer is *more* stable than its keto tautomer because the enol tautomer is aromatic, but the keto tautomer is not (Section 7.8).

keto tautomer — not aromatic; enol tautomer — aromatic

PROBLEM 6♦

Draw the enol tautomer for each of the following compounds:

a. **b.** **c.**

PROBLEM 7♦

Draw the two enol tautomers for the following compound. Which one is more stable?

13.3 KETO–ENOL INTERCONVERSION

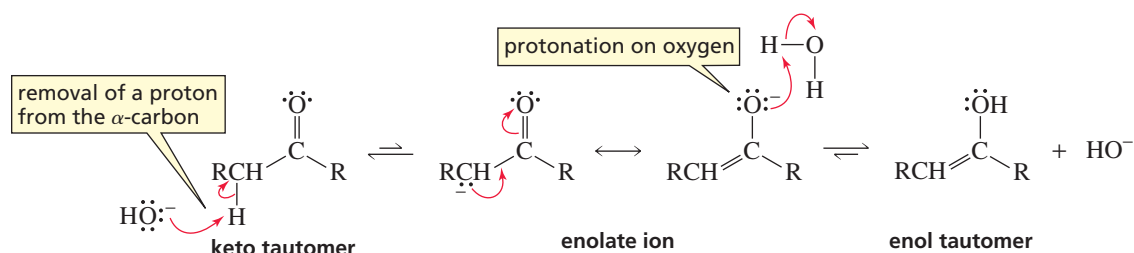
Now that we know that an α-carbon is somewhat acidic, we can better understand why keto and enol tautomers interconvert as we first saw in Section 6.13. **Keto–enol interconversion** (also called **tautomerization**) can be catalyzed by either a base or an acid.

MECHANISM FOR BASE-CATALYZED KETO–ENOL INTERCONVERSION

removal of a proton from the α-carbon

protonation on oxygen

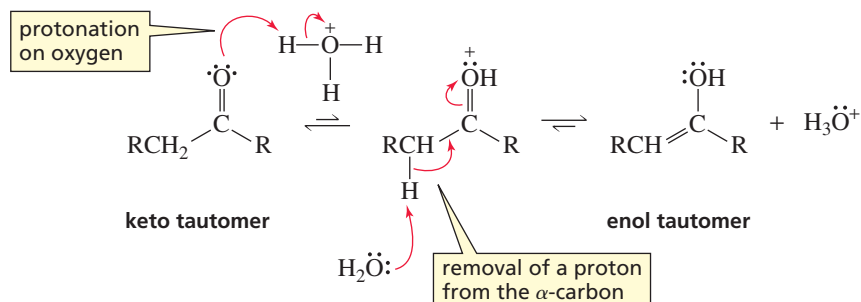
$$RCH_2COR \text{ (keto tautomer)} + HO^- \rightleftharpoons [RC^-HCOR \longleftrightarrow RCH{=}C(O^-)R] \text{ (enolate ion)} \xrightarrow{H_2O} RCH{=}C(OH)R \text{ (enol tautomer)} + HO^-$$

keto tautomer — enolate ion — enol tautomer

- Hydroxide ion removes a proton from the α-carbon of the keto tautomer, forming an anion called an **enolate ion.** The enolate ion has two resonance contributors.
- Protonating the oxygen forms the enol tautomer.

MECHANISM FOR ACID-CATALYZED KETO–ENOL INTERCONVERSION

protonation on oxygen

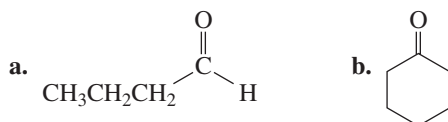
$$RCH_2C(=O)R \;(\text{keto tautomer}) + H_3O^+ \rightleftharpoons RCH_2C(=\overset{+}{O}H)R \;\xrightarrow{H_2O}\; RCH{=}C(OH)R \;(\text{enol tautomer}) + H_3O^+$$

removal of a proton from the α-carbon

- The acid protonates the carbonyl oxygen of the keto tautomer.
- Water removes a proton from the α-carbon, forming the enol tautomer.

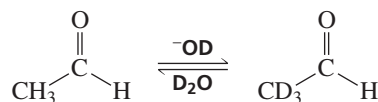
Notice that the steps are reversed in the base- and acid-catalyzed interconversions. In the base-catalyzed reaction, the base removes a proton from an α-carbon in the first step and the oxygen is protonated in the second step. In the acid-catalyzed reaction, the oxygen is protonated in the first step and the proton is removed from the α-carbon in the second step. Notice also that, as expected, the catalyst is regenerated in both the acid- and base-catalyzed reactions.

PROBLEM 8

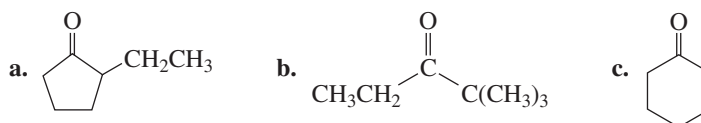
Draw the resonance contributors for the enolate ion that would be formed from each of the following ketones:

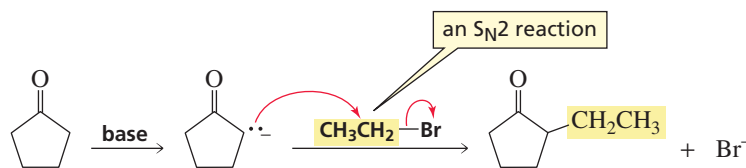
a. $CH_3CH_2CH_2C(=O)H$ **b.** cyclohexanone

PROBLEM 9

When a dilute solution of acetaldehyde in D_2O containing NaOD is shaken, the methyl hydrogens are exchanged with deuterium, but the hydrogen attached to the carbonyl carbon is not. Explain why.

$$CH_3C(=O)H \underset{D_2O}{\overset{^-OD}{\rightleftharpoons}} CD_3C(=O)H$$

PROBLEM 10

Which hydrogens in each of the following compounds would be exchanged with deuterium in a solution of D_2O containing NaOD?

a. 2-ethylcyclopentanone (CH_2CH_3) **b.** $CH_3CH_2C(=O)C(CH_3)_3$ **c.** cyclohexanone

13.4 ALKYLATION OF ENOLATE IONS

Alkylation of the α-carbon of a carbonyl compound is an important reaction because it gives us another way to form a carbon–carbon bond. Alkylation is carried out by first removing a proton from the α-carbon with a base and then adding the appropriate alkyl halide. Because the alkylation is an S_N2 reaction, it works best with primary alkyl halides and methyl halides (Section 8.1).

Enolate ions can be alkylated on the α-carbon.

an S_N2 reaction

base; CH_3CH_2—Br; CH_2CH_3 + Br^-

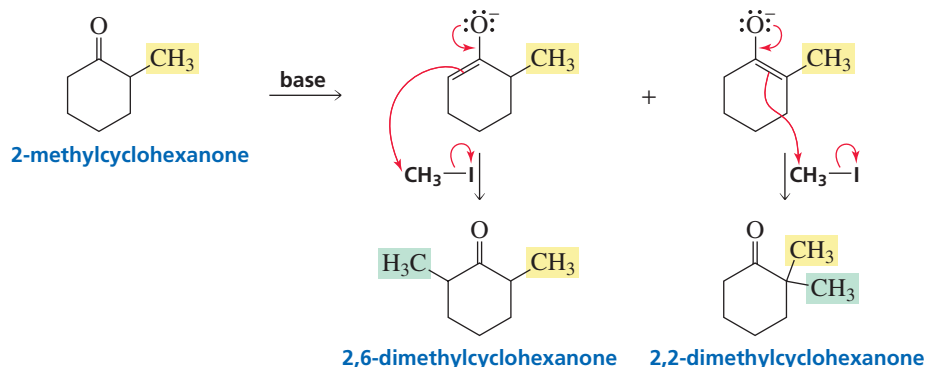
PROBLEM 11

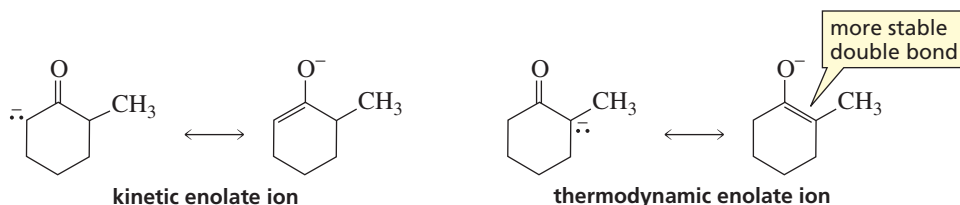
Explain why alkylation of an α-carbon works best if the alkyl halide used in the reaction is a primary alkyl halide, and why alkylation does not work at all if a tertiary alkyl halide is used.

Alkylating Unsymmetrical Ketones

If the ketone is unsymmetrical and has hydrogens on both α-carbons, two monoalkylated products can be obtained because either α-carbon can be alkylated. For example, methylation of 2-methylcyclohexanone with one equivalent of methyl iodide forms both 2,6-dimethylcyclohexanone and 2,2-dimethylcyclohexanone. The relative amounts of the two products depend on the reaction conditions.

2-methylcyclohexanone → base → enolates + CH_3—I

2,6-dimethylcyclohexanone 2,2-dimethylcyclohexanone

The enolate ion leading to 2,6-dimethylcyclohexanone is the ***kinetic* enolate ion** because it is formed faster, since the α-hydrogen that is removed to make this enolate ion is more accessible to the base and it is slightly more acidic. Because 2,6-dimethylcyclohexanone is formed faster, it is the major product if the reaction is carried under conditions (using a strong base such as RNH^-) that causes the reaction to be irreversible.

The kinetic product is the faster formed product.

RNH^- removes a proton from the less substituted α-carbon.

more stable double bond

kinetic enolate ion thermodynamic enolate ion

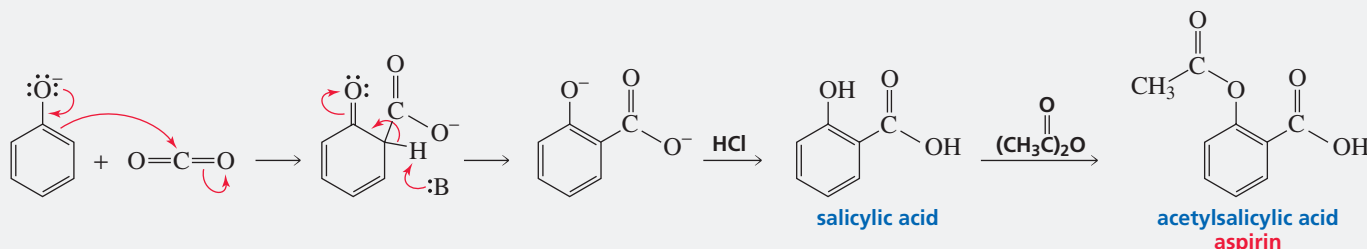
The enolate ion leading to 2,2-dimethylcyclohexanone is the ***thermodynamic* enolate ion** because it is the more stable enolate ion since it has the more substituted double bond. (Alkyl substitution increases enolate ion stability for the same reason that it increases alkene stability; Section 5.6.) Therefore, 2,2-dimethylcyclohexanone is the major product if the reaction is carried under conditions (a relatively weak base such as HO^-) that causes the reaction to be reversible.

The thermodynamic product is the more stable product.

HO^- removes a proton from the more substituted α-carbon.

The Synthesis of Aspirin

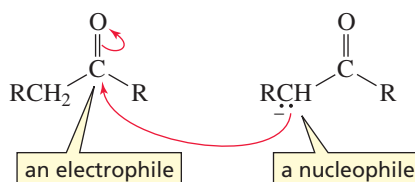
In the first step in the industrial synthesis of aspirin, the phenolate ion reacts with carbon dioxide under pressure to form salicylic acid. Reaction of salicylic acid with acetic anhydride forms acetylsalicylic acid (aspirin).

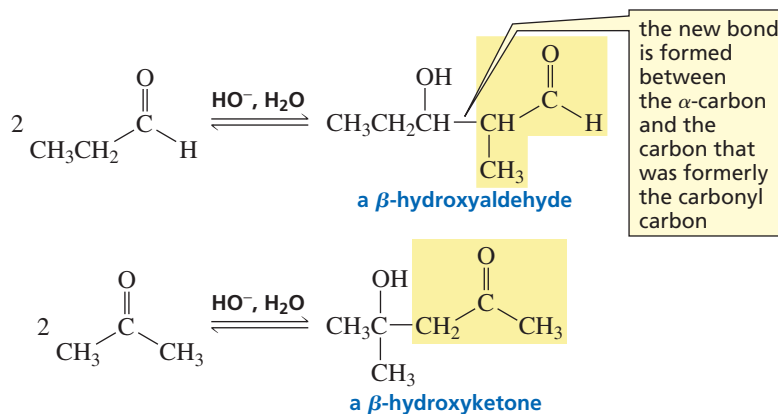
HCl → **salicylic acid** → $(CH_3C)_2O$ → **acetylsalicylic acid** **aspirin**

During World War I, the Bayer Company bought as much phenol as it could on the international market, knowing that eventually all of it could be used to manufacture aspirin. This left little phenol available for other countries to purchase for the synthesis of 2,4,6-trinitrophenol (picric acid), a common explosive at that time.

13.5 AN ALDOL ADDITION FORMS β-HYDROXYALDEHYDES OR β-HYDROXYKETONES

We saw in Chapter 12 that the carbonyl carbon of an aldehyde or a ketone is an electrophile. We have just seen that a proton can be removed from the α-carbon of an aldehyde or a ketone, converting the α-carbon into a nucleophile.

An **aldol addition** is a reaction in which *both* of these reactivities are observed. That is, one molecule of a carbonyl compound—after a proton is removed from an α-carbon—reacts as a *nucleophile* and adds to the *electrophilic* carbonyl carbon of a second molecule of the carbonyl compound.

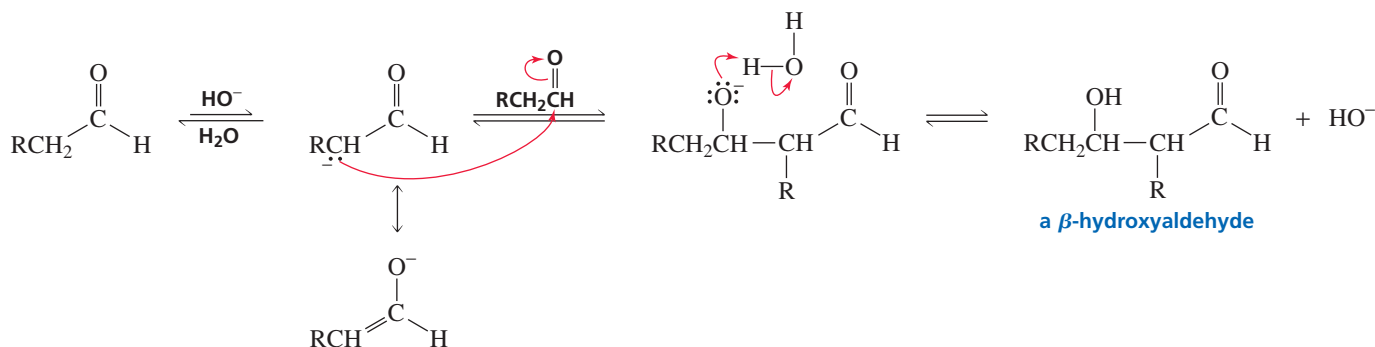
an electrophile — a nucleophile

An Aldol Addition

An aldol addition is a reaction between two molecules of an *aldehyde* or two molecules of a *ketone*. Notice that the reaction forms a new C—C bond that connects the α-carbon of one molecule and the carbon that was originally the carbonyl carbon of the other molecule. That is, the carbon attached to the alcohol group (OH) is adjacent to the carbon attached to the aldehyde group (CH=O).

An aldol addition forms a β-hydroxyaldehyde or a β-hydroxyketone.

When the reactant is an aldehyde, the product is a **β-hydroxyaldehyde,** which is why the reaction is called an aldol addition ("ald" for *aldehyde*, "ol" for *alcohol*). When the reactant is a ketone, the product is a **β-hydroxyketone.** (Note that an OH group is called hydroxy when it is a substituent in a carbonyl compound.)

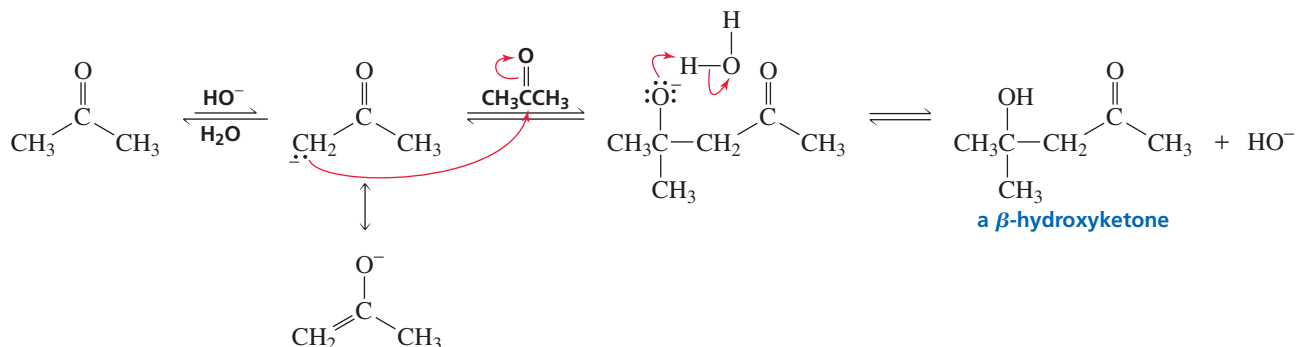
MECHANISM FOR THE ALDOL ADDITION

$$RCH_2CHO \underset{H_2O}{\overset{HO^-}{\rightleftharpoons}} \overset{-}{R\ddot{C}H}CHO \longleftrightarrow RCH{=}C(O^-)H \;\overset{RCH_2CHO}{\rightleftharpoons}\; RCH_2CH(O^-)\!-\!CH(R)CHO \;\overset{H_2O}{\rightleftharpoons}\; RCH_2CH(OH)\!-\!CH(R)CHO + HO^-$$

a β-hydroxyaldehyde

- A base removes a proton from the α-carbon, creating an enolate ion.
- The enolate ion adds to the carbonyl carbon of a second molecule of the carbonyl compound.
- The negatively charged oxygen is protonated.

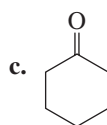
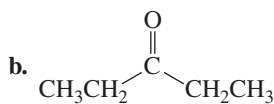
A ketone forms an aldol addition product by the same mechanism.

$$CH_3COCH_3 \underset{H_2O}{\overset{HO^-}{\rightleftharpoons}} \overset{-}{\ddot{C}H_2}COCH_3 \longleftrightarrow CH_2{=}C(O^-)CH_3 \;\overset{CH_3COCH_3}{\rightleftharpoons}\; CH_3C(O^-)(CH_3)\!-\!CH_2COCH_3 \;\overset{H_2O}{\rightleftharpoons}\; CH_3C(OH)(CH_3)\!-\!CH_2COCH_3 + HO^-$$

a β-hydroxyketone

Notice that the aldol addition is a nucleophilic addition reaction. It is just like the nucleophilic addition reactions that aldehydes and ketones undergo with other carbon nucleophiles (Section 12.5). Because an aldol addition occurs between two molecules of the same carbonyl compound, the product has twice as many carbons as the reacting aldehyde or ketone.

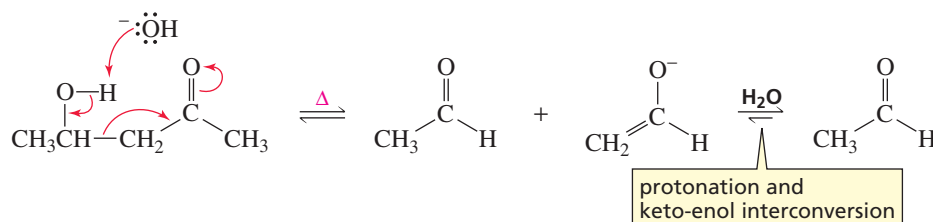
PROBLEM 12

What aldol addition product is formed from each of the following compounds?

a. $CH_3CH_2CH_2CH_2CHO$ **b.** $CH_3CH_2COCH_2CH_3$ **c.** cyclohexanone

A Retro-Aldol Addition

Because an aldol addition is reversible, when the product of an aldol addition (the β-hydroxyaldehyde or β-hydroxyketone) is heated with hydroxide ion and water, the aldehyde or ketone that formed the aldol addition product can be regenerated.

$$CH_3CH(OH)CH_2COCH_3 \xrightleftharpoons{\Delta} CH_3CHO + {}^-OCH=CH_2 \xrightleftharpoons{H_2O} CH_3CHO$$

protonation and keto-enol interconversion

PROBLEM 13♦

What aldehyde or ketone would be obtained when each of the following compounds is heated in a basic aqueous solution?

a. 2-ethyl-3-hydroxyhexanal **b.** 5-ethyl-5-hydroxy-4-methyl-3-heptanone

13.6 THE DEHYDRATION OF ALDOL ADDITION PRODUCTS FORMS α,β-UNSATURATED ALDEHYDES AND KETONES

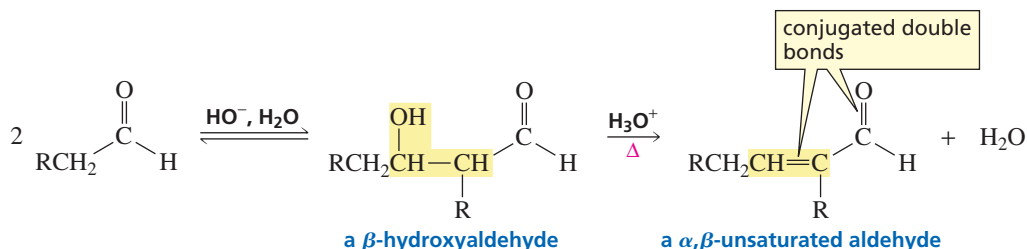
We have seen that alcohols dehydrate when they are heated with acid (Section 9.4). The β-hydroxyaldehyde and β-hydroxyketone products of aldol addition reactions are easier to dehydrate than many other alcohols, because the double bond formed when the compound is dehydrated is conjugated with a carbonyl group. Conjugation increases the stability of the product and, therefore, makes it easier to form (Section 7.7).

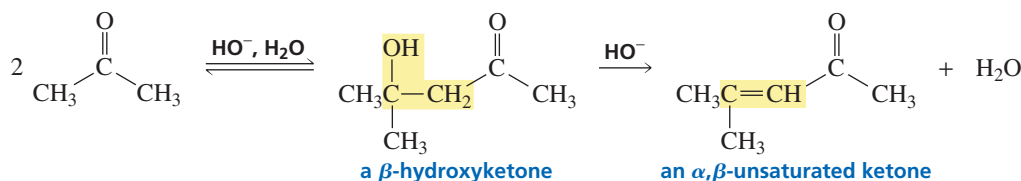
When the product of an aldol addition is dehydrated, the overall reaction is called an **aldol condensation.** A **condensation reaction** is a reaction that combines two molecules by forming a new C—C bond while removing a small molecule. In an aldol addition, water is the small molecule that is removed. Notice that an aldol condensation forms an ***α,β*-unsaturated aldehyde** or an ***α,β*-unsaturated ketone.**

An aldol addition product loses water to form an aldol condensation product.

$$2\ RCH_2CHO \xrightleftharpoons{HO^-,\ H_2O} RCH_2CH(OH)CH(R)CHO \xrightarrow[\Delta]{H_3O^+} RCH_2CH{=}C(R)CHO + H_2O$$

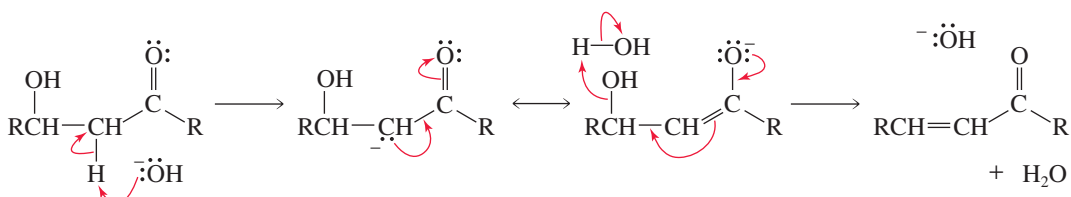
a β-hydroxyaldehyde a α,β-unsaturated aldehyde

conjugated double bonds

Unlike alcohols that can be dehydrated only under acidic conditions, β-hydroxyaldehydes and β-hydroxyketones can also be dehydrated under basic conditions if the reaction is carried out with excess hydroxide ion.

An aldol condensation forms an α,β-unsaturated aldehyde or an α,β-unsaturated ketone.

$$2\ CH_3COCH_3 \xrightleftharpoons{HO^-,\ H_2O} CH_3C(OH)(CH_3)CH_2COCH_3 \xrightarrow{HO^-} CH_3C(CH_3){=}CHCOCH_3 + H_2O$$

a β-hydroxyketone an α,β-unsaturated ketone

MECHANISM FOR BASE-CATALYZED DEHYDRATION

$$RCH(OH)CH(H)COR + {}^-OH \longrightarrow RCH(OH)\bar{C}HCOR \longleftrightarrow RCH(OH)CH{=}C(O^-)R \;(+\ H{-}OH) \longrightarrow RCH{=}CHCOR + {}^-OH + H_2O$$

- Hydroxide ion removes a proton from the α-carbon, thereby forming an enolate ion.
- The enolate ion eliminates the OH group, which picks up a proton as it leaves, thereby making it a weaker base and, therefore, a better leaving group.

PROBLEM 14

What product is obtained from the aldol condensation of cyclohexanone?

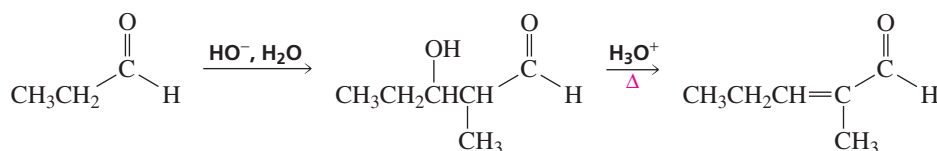
PROBLEM 15 Solved

How could you prepare the following compounds using a starting material containing no more than three carbons?

a. $CH_3CH_2CH{=}C(CH_3)CHO$

b. CH_3COCH_2CHO

Solution to 15a A compound with the correct six-carbon skeleton can be obtained if a three-carbon aldehyde undergoes an aldol addition. Dehydration of the addition product forms the desired α,β-unsaturated aldehyde.

$$CH_3CH_2CHO \xrightarrow{HO^-,\ H_2O} CH_3CH_2CH(OH)CH(CH_3)CHO \xrightarrow[\Delta]{H_3O^+} CH_3CH_2CH{=}C(CH_3)CHO$$

13.7 A CROSSED ALDOL ADDITION

If two different carbonyl compounds are used in an aldol addition—known as a **crossed aldol addition**—four products can be formed because reaction with hydroxide ion can form two different enolate ions ($\mathbf{A}^-$ and $\mathbf{B}^-$) and each enolate ion can react with either of the two carbonyl compounds (**A** or **B**). A reaction that forms four products clearly is not a synthetically useful reaction.

$$\underset{\mathbf{A}}{CH_3CH_2CHO} + \underset{\mathbf{B}}{CH_3CHO}$$

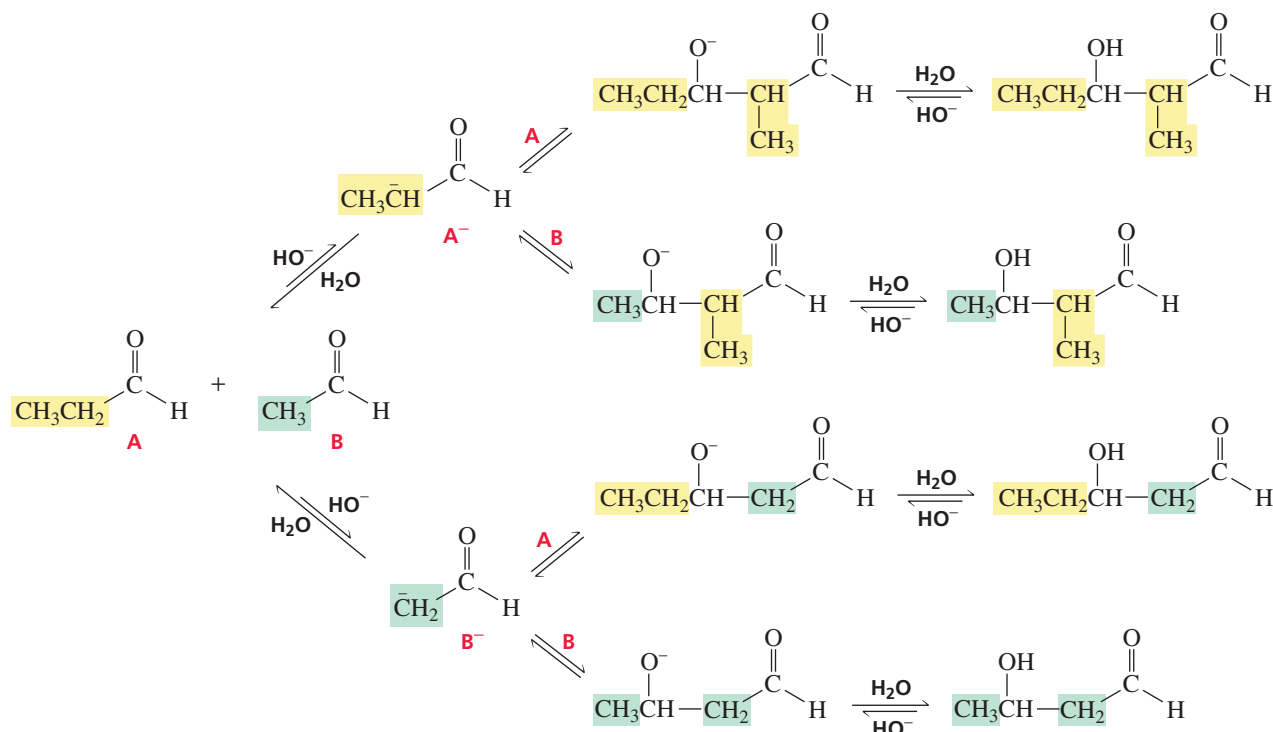
$$\xrightleftharpoons[H_2O]{HO^-} \underset{\mathbf{A}^-}{CH_3\bar{C}HCHO}$$

With A: $CH_3CH_2CH(O^-)CH(CH_3)CHO \xrightleftharpoons[HO^-]{H_2O} CH_3CH_2CH(OH)CH(CH_3)CHO$

With B: $CH_3CH(O^-)CH(CH_3)CHO \xrightleftharpoons[HO^-]{H_2O} CH_3CH(OH)CH(CH_3)CHO$

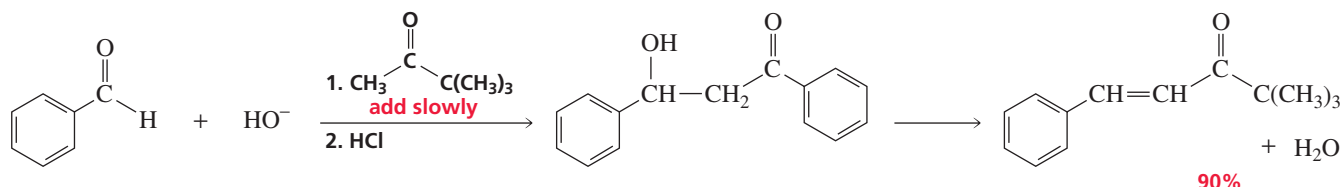
$$\xrightleftharpoons[H_2O]{HO^-} \underset{\mathbf{B}^-}{\bar{C}H_2CHO}$$

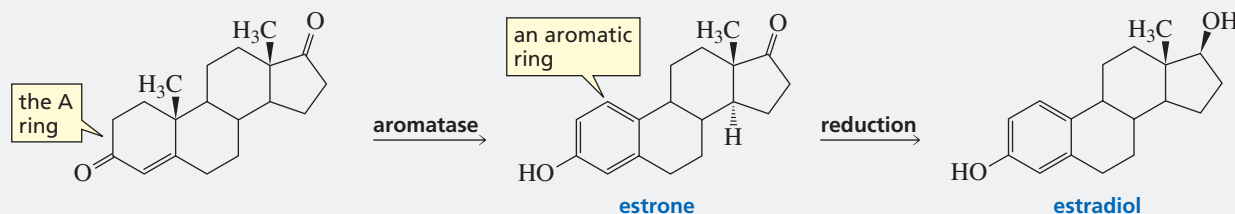
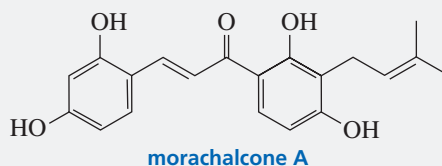
With A: $CH_3CH_2CH(O^-)CH_2CHO \xrightleftharpoons[HO^-]{H_2O} CH_3CH_2CH(OH)CH_2CHO$

With B: $CH_3CH(O^-)CH_2CHO \xrightleftharpoons[HO^-]{H_2O} CH_3CH(OH)CH_2CHO$

If one of the carbonyl compounds does not have any α-hydrogens, then the compound with α-hydrogens is added slowly to a solution of the compound without α-hydrogens and a base.

Primarily one product can be obtained from a crossed aldol addition if one of the aldehydes does not have any α-hydrogens and, therefore, cannot form an enolate ion. That cuts the possible products from four to two. Then, if the aldehyde with α-hydrogens is added slowly to a solution of the aldehyde without α-hydrogens and hydroxide ion, the chance that the aldehyde with α-hydrogens, after forming an enolate ion, will react with another molecule of its parent carbonyl compound will be minimized, so the possible products are cut to essentially one. The aldol addition product formed in this reaction loses water as soon as it is formed because the new double bond is conjugated not only with the carbonyl group but also with the benzene ring. (Recall that the more stable the alkene, the easier it is formed.)

1. $CH_3C(=O)C(CH_3)_3$, add slowly; 2. HCl

PhCHO + HO^- → PhCH(OH)–CH_2–C(=O)Ph → PhCH=CH–C(=O)–$C(CH_3)_3$ + H_2O (90%)

Breast Cancer and Aromatase Inhibitors

Current statistics show that one in eight women will develop breast cancer. Men also get breast cancer but are 100 times less likely to do so than women. There are several different types of tumors that cause breast cancer, some of which are estrogen dependent. An estrogen-dependent tumor has receptors that bind estrogen. Without estrogen, the tumor cannot grow.

The A ring (the ring on the left) of estrogen hormones (estrone and estradiol) is an aromatic phenol (Section 3.14). One of the last steps in the biosynthesis of estrogen hormones from cholesterol is catalyzed by an enzyme called aromatase. Aromatase catalyzes the reaction that causes the A ring to become aromatic. Therefore, one approach to the treatment of breast cancer is to administer drugs that will inhibit aromatase. If aromatase is inhibited, the estrogen hormones cannot be synthesized, but the biosynthesis of other important hormones from cholesterol will not be affected. There are several aromatase inhibitors on the market, and scientists continue to search for more potent ones. Fifteen different aromatase inhibitors have been isolated from the leaves of the paper mulberry tree, one of which is morachalcone A (see chapter opening photo).

morachalcone A

PROBLEM 16

What two carbonyl compounds are required for the synthesis of morachalcone A (the aromatase inhibitor discussed in the box above)?

13.8 A CLAISEN CONDENSATION FORMS A β-KETO ESTER

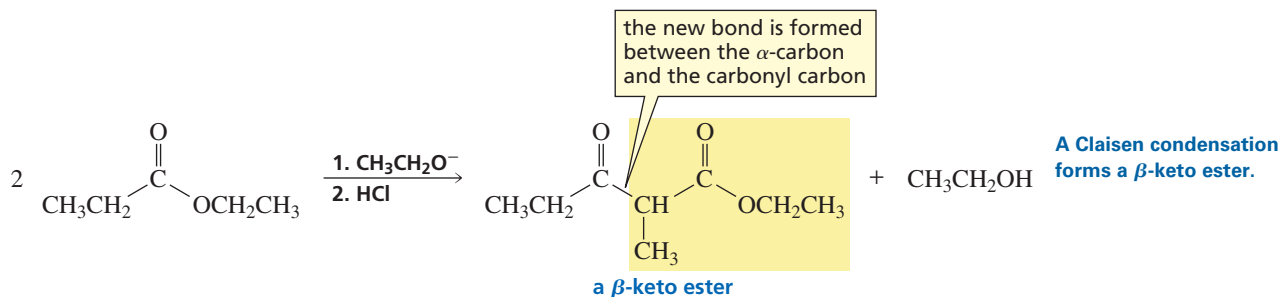
When two molecules of an *ester* undergo a condensation reaction, the reaction is called a **Claisen condensation.** The product of a Claisen condensation is a ***β*-keto ester.**

In a Claisen condensation, as in an aldol addition, one molecule of carbonyl compound is the nucleophile and a second molecule is the electrophile. And, as in an aldol addition, the new C—C bond connects the α-carbon of one molecule to the carbon that was formerly the carbonyl carbon of the other molecule. In a Claisen condensation, an alcohol is the small molecule that is removed.

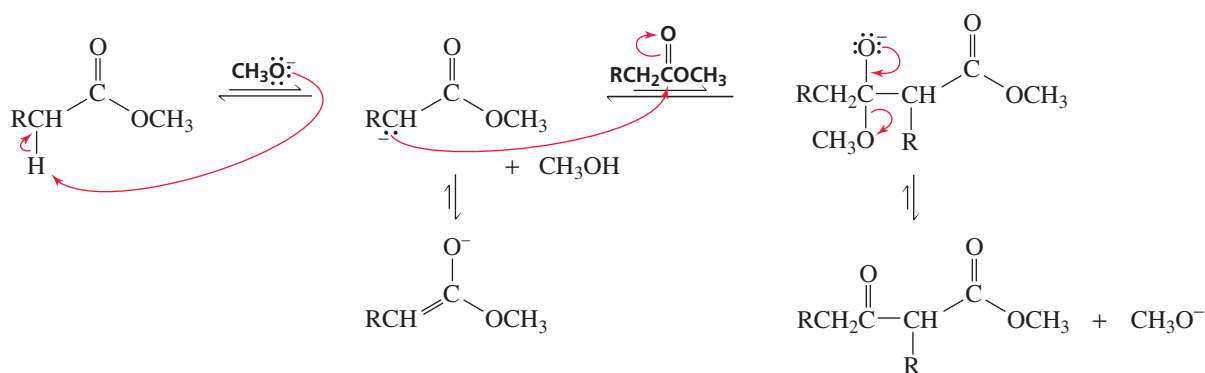
$$2\ CH_3CH_2COOCH_2CH_3 \xrightarrow[\text{2. HCl}]{\text{1. } CH_3CH_2O^-} CH_3CH_2COCH(CH_3)COOCH_2CH_3 + CH_3CH_2OH$$

the new bond is formed between the α-carbon and the carbonyl carbon

a β-keto ester

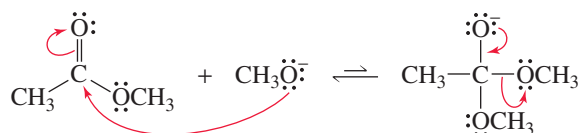
A Claisen condensation forms a β-keto ester.

MECHANISM FOR THE CLAISEN CONDENSATION

$$RCH(H)COOCH_3 \underset{CH_3O^-}{\rightleftharpoons} R\overset{-}{C}HCOOCH_3 + CH_3OH \xrightleftharpoons{RCH_2COCH_3 (=O)} RCH_2C(O^-)(OCH_3)\text{—}CH(R)COOCH_3 \rightleftharpoons RCH_2C(=O)\text{—}CH(R)COOCH_3 + CH_3O^-$$

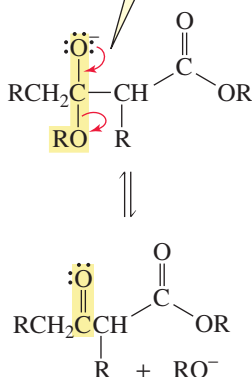
$$R\overset{-}{C}HCOOCH_3 \rightleftharpoons RCH{=}C(O^-)OCH_3$$

- A base removes a proton from the α-carbon, creating an enolate ion. The base employed corresponds to the leaving group of the ester.
- The enolate ion adds to the carbonyl carbon of a second molecule of the ester, forming a tetrahedral intermediate.
- The carbon-oxygen π bond re-forms, eliminating an alkoxide ion.

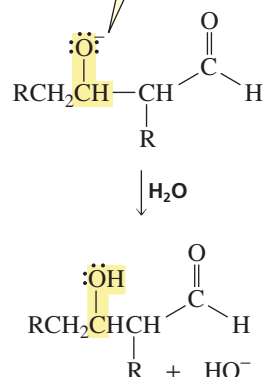
Thus, like the reaction of esters with other nucleophiles, the Claisen condensation is a nucleophilic acyl substitution reaction (Section 11.5).

The base used to remove the proton from the α-carbon in a Claisen condensation should be the same as the leaving group of the ester, so the reactant will not change if the base were to add to the carbonyl group.

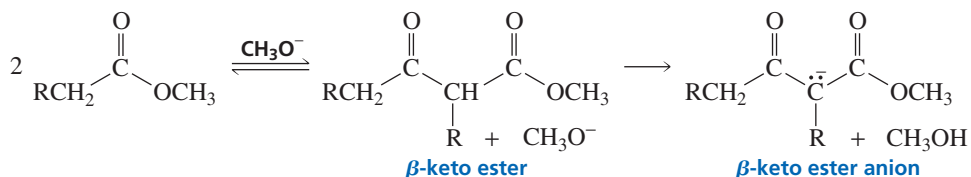
$$CH_3COOCH_3 + CH_3O^- \rightleftharpoons CH_3\text{—}C(O^-)(OCH_3)\text{—}OCH_3$$

Notice that, after nucleophilic addition, the Claisen condensation and the aldol addition reactions differ. In the Claisen condensation, the negatively charged oxygen re-forms the carbon–oxygen π bond and eliminates the $^-$OR group. In the aldol addition, the negatively charged oxygen obtains a proton from the solvent.

Claisen condensation — formation of a π bond by elimination of RO^-

$$RCH_2C(O^-)(OR)-CH(R)-C(=O)OR \rightleftharpoons RCH_2C(=O)CH(R)C(=O)OR + RO^-$$

aldol addition — protonation of O^-

$$RCH_2CH(O^-)-CH(R)-C(=O)H \xrightarrow{H_2O} RCH_2CH(OH)CH(R)C(=O)H + HO^-$$

The last step of the Claisen condensation is different than the last step of the aldol addition because the carbon bonded to the negatively charged oxygen in an ester is also bonded to a group that can be eliminated, whereas the carbon bonded to the negatively charged oxygen in an aldehyde or a ketone is not bonded to such a group. Thus, the Claisen condensation is a nucleophilic acyl substitution reaction, whereas the aldol addition is a nucleophilic addition reaction.

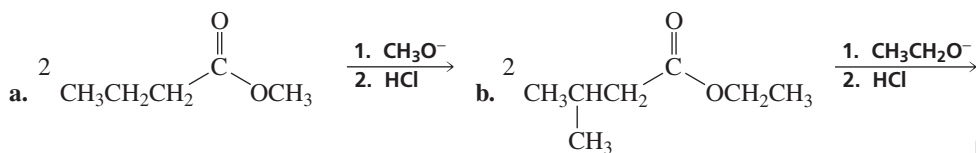
The Claisen condensation is reversible and favors the reactant since it is more stable than the product (β-keto ester). However, the condensation reaction can be driven to completion if a proton is removed from the β-keto ester (Le Châtelier's principle; Section 5.5). A proton is easily removed because the central α-carbon of the β-keto ester is flanked by two carbonyl groups, making its α-hydrogen much more acidic than the α-hydrogen of the ester.

$$2\ RCH_2C(=O)OCH_3 \overset{CH_3O^-}{\rightleftharpoons} \underset{\beta\text{-keto ester}}{RCH_2C(=O)CH(R)C(=O)OCH_3} + CH_3O^- \longrightarrow \underset{\beta\text{-keto ester anion}}{RCH_2C(=O)\ddot{C}^-(R)C(=O)OCH_3} + CH_3OH$$

Consequently, a successful Claisen condensation requires an ester with two α-hydrogens. When the reaction is over, addition of acid to the reaction mixture reprotonates the β-keto ester anion and protonates the alkoxide ion, so the reverse reaction cannot occur.

PROBLEM 17♦

Draw the products of the following reactions:

a. $2\ CH_3CH_2CH_2C(=O)OCH_3 \xrightarrow[\text{2. HCl}]{\text{1. } CH_3O^-}$

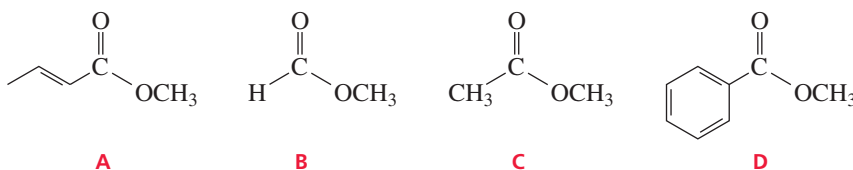
b. $2\ CH_3CH(CH_3)CH_2C(=O)OCH_2CH_3 \xrightarrow[\text{2. HCl}]{\text{1. } CH_3CH_2O^-}$

PROBLEM 18♦

Which of the following esters cannot undergo a Claisen condensation?

A: $CH_3CH=CHC(=O)OCH_3$

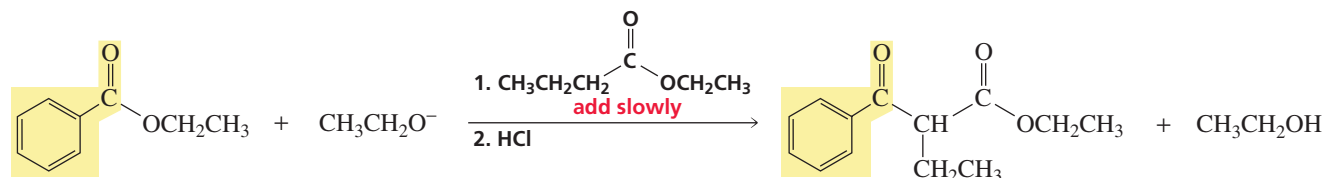
B: $HC(=O)OCH_3$

C: $CH_3C(=O)OCH_3$

D: $C_6H_5C(=O)OCH_3$

A Crossed Claisen Condensation

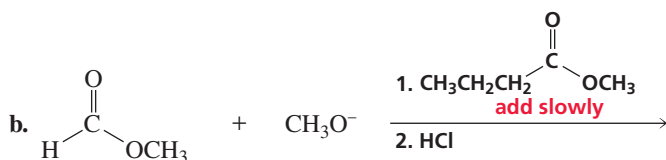
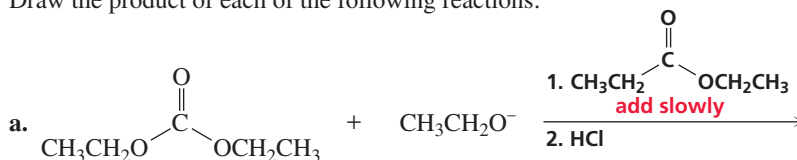
A **crossed Claisen condensation** is a condensation reaction between two different esters. Like a crossed aldol addition, a crossed Claisen condensation is a useful reaction only if it is carried out under conditions that foster the formation of primarily one product. Otherwise, the reaction will form a mixture of products that are difficult to separate.

Primarily one product will be formed from a crossed Claisen condensation if one of the esters has no α-hydrogens (and, therefore, cannot form an enolate ion) and the ester with α-hydrogens is added slowly to a solution of the ester without α-hydrogens and the alkoxide ion.

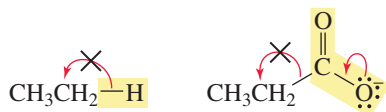
$$C_6H_5COOCH_2CH_3 + CH_3CH_2O^- \xrightarrow[\text{2. HCl}]{\text{1. } CH_3CH_2CH_2COOCH_2CH_3 \text{ add slowly}} C_6H_5COCH(CH_2CH_3)COOCH_2CH_3 + CH_3CH_2OH$$

PROBLEM 19

Draw the product of each of the following reactions:

a. $$CH_3CH_2OCOOCH_2CH_3 + CH_3CH_2O^- \xrightarrow[\text{2. HCl}]{\text{1. } CH_3CH_2COOCH_2CH_3 \text{ add slowly}}$$

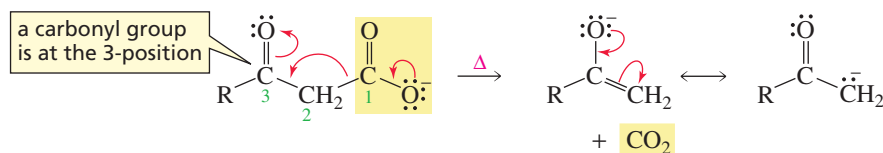
b. $$HCOOCH_3 + CH_3O^- \xrightarrow[\text{2. HCl}]{\text{1. } CH_3CH_2CH_2COOCH_3 \text{ add slowly}}$$

13.9 CO₂ CAN BE REMOVED FROM A CARBOXYLIC ACID WITH A CARBONYL GROUP AT THE 3-POSITION

Carboxylate ions do not lose CO_2, for the same reason that alkanes such as ethane do not lose a proton—namely, the leaving group would be a carbanion. Carbanions are very strong bases, which makes them very poor leaving groups.

$$CH_3CH_2\text{—}H \qquad CH_3CH_2\text{—}COO^-$$

If, however, the CO_2 group is attached to a carbon that is adjacent to a carbonyl carbon, the CO_2 group can be removed, because the electrons left behind can be delocalized onto the carbonyl oxygen. Consequently, carboxylate ions with a carbonyl group at the 3-position lose CO_2 when they are heated. Loss of CO_2 from a molecule is called **decarboxylation.**

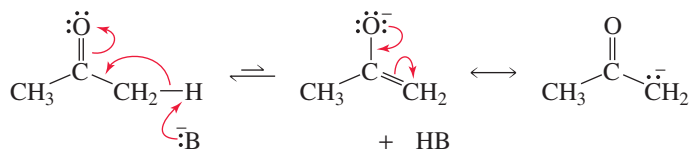
removing CO_2 from an α-carbon

a carbonyl group is at the 3-position

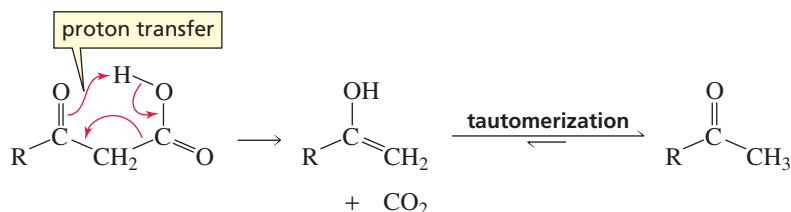
$$RCOCH_2COO^- \xrightarrow{\Delta} RC(O^-)\text{=}CH_2 \longleftrightarrow RCO\overset{-}{C}H_2 + CO_2$$

A carboxylic acid with a carbonyl group at the 3-position decarboxylates when heated.

Notice the similarity between removing CO_2 from an α-carbon and removing a proton from an α-carbon. In both reactions, when the substituent—CO_2 in one case, H^+ in the other—is removed, the electrons left behind are delocalized onto an oxygen.

removing a proton from an α-carbon

$$CH_3C(=O)CH_2{-}H + {:}B^- \rightleftharpoons CH_3C(O^-)=CH_2 \longleftrightarrow CH_3C(=O)\ddot{C}H_2^- \quad + \ HB$$

Decarboxylation is even easier under acidic conditions because the reaction is catalyzed by the transfer of a proton from the carboxyl group to the carbonyl oxygen. The enol that is formed immediately tautomerizes to a ketone.

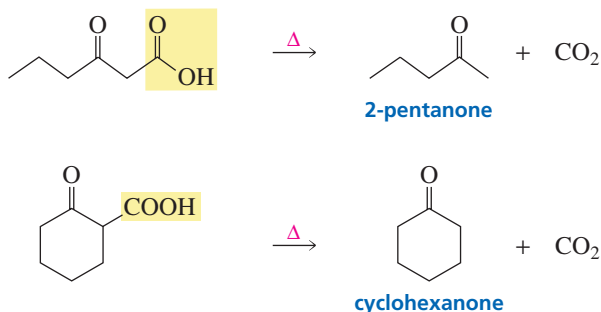
proton transfer

$$RC(=O)CH_2C(=O)OH \longrightarrow RC(OH)=CH_2 + CO_2 \xrightarrow{\text{tautomerization}} RC(=O)CH_3$$

In summary, carboxylic acids with a carbonyl group at the 3-position lose CO_2 when they are heated.

$$CH_3CH_2CH_2C(=O)CH_2COOH \xrightarrow{\Delta} \text{2-pentanone} + CO_2$$

2-pentanone

$$\text{2-oxocyclohexanecarboxylic acid (COOH)} \xrightarrow{\Delta} \text{cyclohexanone} + CO_2$$

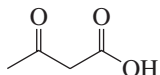
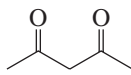
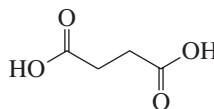
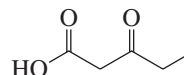
cyclohexanone

PROBLEM 20♦

Which of the following compounds would be expected to decarboxylate when heated?

A: $CH_3C(=O)CH_2C(=O)OH$

B: $CH_3C(=O)CH_2C(=O)CH_3$

C: $HOC(=O)CH_2CH_2C(=O)OH$

D: $HOC(=O)CH_2C(=O)CH_2CH_3$

13.10 REACTIONS AT THE α-CARBON IN CELLS

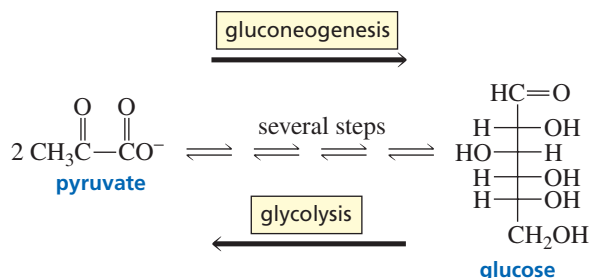
Many reactions that occur in cells involve reactions at the α-carbon—that is, the kinds of reactions you have been studying in this chapter. We will now look at a few examples.

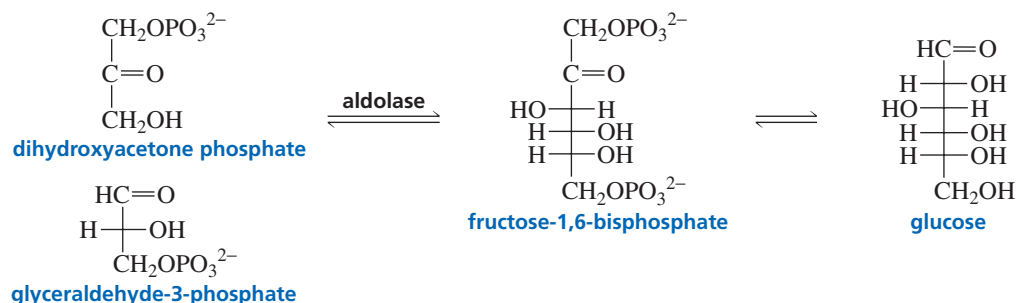
A Biological Aldol Addition

Glucose, the most abundant sugar found in nature, is synthesized in cells from two molecules of pyruvate. The series of reactions that convert two molecules of pyruvate into glucose is called **gluconeogenesis** (Section 19.11). The reverse process—the breakdown of glucose into two molecules of pyruvate—is called **glycolysis** (Section 19.5).

gluconeogenesis

$$2\ CH_3\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}O^- \underset{\text{glycolysis}}{\overset{\text{several steps}}{\rightleftharpoons\ \rightleftharpoons\ \rightleftharpoons\ \rightleftharpoons}} \text{glucose}$$

pyruvate → glucose (HC=O; H–C–OH; HO–C–H; H–C–OH; H–C–OH; CH_2OH)

Because glucose has twice as many carbons as pyruvate, you should not be surprised to learn that one of the steps in the biosynthesis of glucose is an aldol addition. An enzyme called aldolase catalyzes an aldol addition between dihydroxyacetone phosphate and glyceraldehyde-3-phosphate. The product is fructose-1,6-bisphosphate, which is subsequently converted to glucose.

dihydroxyacetone phosphate ($CH_2OPO_3^{2-}$; C=O; CH_2OH) + glyceraldehyde-3-phosphate (HC=O; H–C–OH; $CH_2OPO_3^{2-}$) $\overset{\text{aldolase}}{\rightleftharpoons}$ fructose-1,6-bisphosphate ($CH_2OPO_3^{2-}$; C=O; HO–C–H; H–C–OH; H–C–OH; $CH_2OPO_3^{2-}$) $\rightleftharpoons$ glucose (HC=O; H–C–OH; HO–C–H; H–C–OH; H–C–OH; CH_2OH)

PROBLEM 21

Propose a mechanism for the formation of fructose-1,6-bisphosphate from dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, using hydroxide ion as the catalyst.

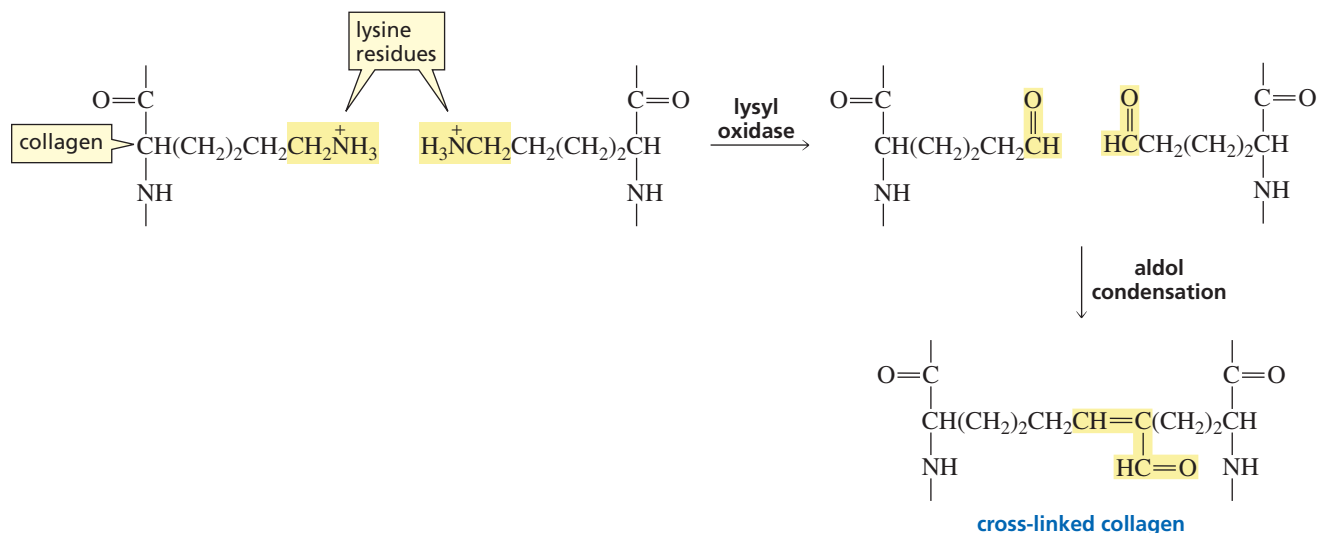
A Biological Aldol Condensation

Collagen is the most abundant protein in mammals, amounting to about one-fourth of the total protein. It is the major fibrous component of bone, teeth, skin, cartilage, and tendons. Individual collagen molecules—called tropocollagen—can be isolated only from tissues of young animals. As animals age, the individual collagen molecules become cross-linked, which is why meat from older animals is tougher than meat from younger ones. Collagen cross-linking is an example of an aldol condensation.

collagen: $O{=}C$–$CH(CH_2)_2CH_2CH_2\overset{+}{N}H_3$ (NH)   lysine residues $H_3\overset{+}{N}CH_2CH_2(CH_2)_2CH$–$C{=}O$ (NH)

$\xrightarrow{\text{lysyl oxidase}}$ $O{=}C$–$CH(CH_2)_2CH_2\overset{O}{\overset{\|}{C}}H$ (NH) $H\overset{O}{\overset{\|}{C}}CH_2(CH_2)_2CH$–$C{=}O$ (NH)

$\xrightarrow{\text{aldol condensation}}$ $O{=}C$–$CH(CH_2)_2CH_2CH{=}C(CH_2)_2CH$–$C{=}O$, with $HC{=}O$ on the C of the double bond (NH, NH)

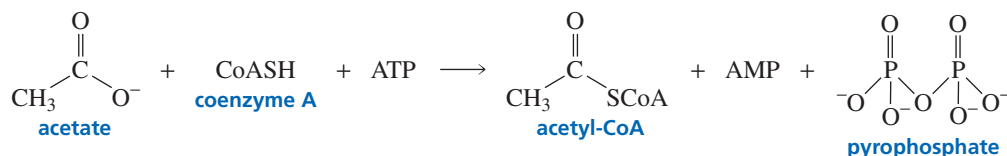
cross-linked collagen

Before collagen molecules can cross-link, the primary amino groups of the lysine residues of collagen must be converted to aldehyde groups. (Lysine is an amino acid; Section 17.1) The enzyme that catalyzes this reaction is called lysyl oxidase. An aldol condensation between two aldehyde groups results in a cross-linked protein.

A Biological Claisen Condensation

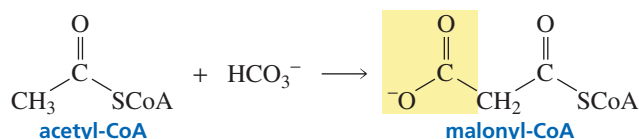
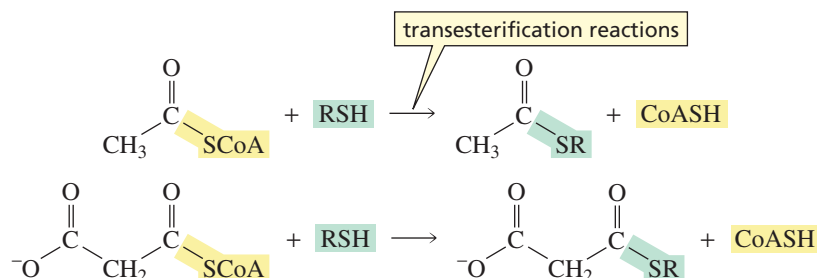
Naturally occurring fatty acids are long, unbranched carboxylic acids that contain an even number of carbons (Section 20.1) because they are synthesized from acetate, a compound with two carbons.

In Section 11.6, you saw that carboxylic acids can be activated in cells by being converted to thioesters of coenzyme A.

$$CH_3C(=O)O^- + CoASH + ATP \longrightarrow CH_3C(=O)SCoA + AMP + {}^-O-P(=O)(O^-)-O-P(=O)(O^-)-O^-$$

acetate; coenzyme A; acetyl-CoA; pyrophosphate

One of the necessary reactants for fatty acid synthesis is malonyl-CoA, which is obtained by carboxylation of acetyl-CoA (Section 18.10).

$$CH_3C(=O)SCoA + HCO_3^- \longrightarrow {}^-OC(=O)CH_2C(=O)SCoA$$

acetyl-CoA; malonyl-CoA

Before fatty acid synthesis can occur, the acyl groups of acetyl-CoA and malonyl-CoA are transferred to other thiols by means of a transesterification reaction.

transesterification reactions

$$CH_3C(=O)SCoA + RSH \longrightarrow CH_3C(=O)SR + CoASH$$

$$^-OC(=O)CH_2C(=O)SCoA + RSH \longrightarrow {}^-OC(=O)CH_2C(=O)SR + CoASH$$

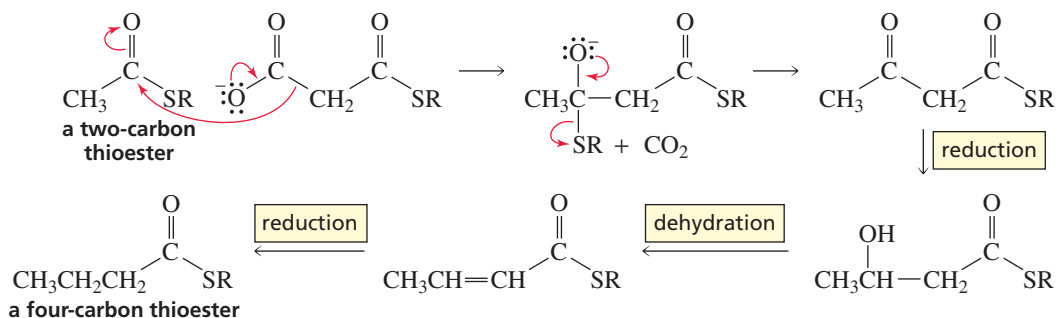
A molecule of acetyl thioester and a molecule of malonyl thioester are the reactants for the first round of the biosynthesis of a fatty acid.

STEPS IN FATTY ACID BIOSYNTHESIS

$$CH_3C(=O)SR + {}^-OC(=O)CH_2C(=O)SR \longrightarrow CH_3C(O^-)(SR)-CH_2C(=O)SR \longrightarrow CH_3C(=O)CH_2C(=O)SR + {}^-SR + CO_2$$

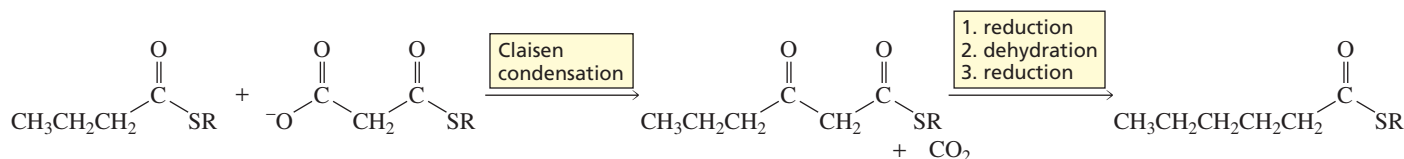
a two-carbon thioester

$$CH_3C(=O)CH_2C(=O)SR \xrightarrow{\text{reduction}} CH_3CH(OH)-CH_2C(=O)SR \xrightarrow{\text{dehydration}} CH_3CH{=}CHC(=O)SR \xrightarrow{\text{reduction}} CH_3CH_2CH_2C(=O)SR$$

a four-carbon thioester

- The first step is a Claisen condensation. The nucleophile needed for a Claisen condensation is obtained by removing CO_2—rather than a proton—from the α-carbon of malonyl thioester. (Recall that a carboxylic acid with a carbonyl group at the 3-position is easily decarboxylated; Section 13.8.) Loss of CO_2 also drives the reaction to completion.

- The product of the condensation reaction undergoes a reduction, a dehydration, and a second reduction to form a four-carbon thioester. (Recall that a ketone is easier to reduce than an ester; Section 12.7.) Each reaction is catalyzed by a different enzyme.

The four-carbon thioester and another molecule of malonyl thioester are the reactants for the second round of the biosynthesis.

$$CH_3CH_2CH_2C(=O)SR + {}^{-}OC(=O)CH_2C(=O)SR \xrightarrow{\text{Claisen condensation}} CH_3CH_2CH_2C(=O)CH_2C(=O)SR + CO_2 \xrightarrow{\text{1. reduction; 2. dehydration; 3. reduction}} CH_3CH_2CH_2CH_2CH_2C(=O)SR$$

- Again, the product of the Claisen condensation undergoes a reduction, a dehydration, and a second reduction—this time to form a six-carbon thioester.
- The sequence of reactions is repeated, and each time two more carbons are added to the chain.

PROBLEM 22♦

Palmitic acid is a straight-chain saturated 16-carbon fatty acid. How many moles of malonyl-CoA are required for the synthesis of one mole of palmitic acid?

PROBLEM 23♦

a. If the biosynthesis of palmitic acid were carried out with CD_3COSR and nondeuterated malonyl thioester, how many deuterium atoms would be incorporated into palmitic acid?
b. If the biosynthesis of palmitic acid were carried out with $^{-}OOCCD_2COSR$ and nondeuterated acetyl thioester, how many deuterium atoms would be incorporated into palmitic acid?

A Biological Decarboxylation

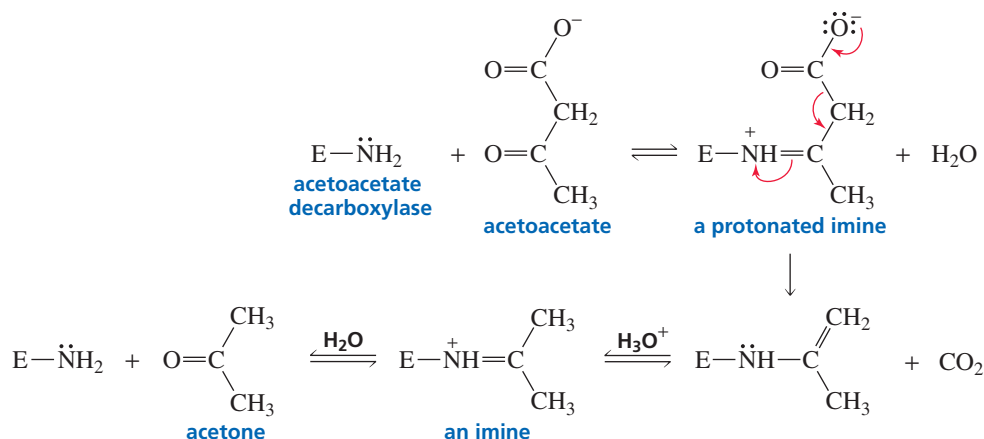
An example of a decarboxylation reaction that occurs in cells is the decarboxylation of acetoacetate.

$$E{-}\ddot{N}H_2 + O{=}C(CH_3)CH_2C(=O)O^{-} \rightleftharpoons E{-}\overset{+}{N}H{=}C(CH_3)CH_2C(=O)O^{-} + H_2O$$

acetoacetate decarboxylase; acetoacetate; a protonated imine

$$\downarrow$$

$$E{-}\ddot{N}H{-}C(CH_3){=}CH_2 + CO_2 \xrightleftharpoons{H_3O^+} E{-}\overset{+}{N}H{=}C(CH_3)_2 \xrightleftharpoons{H_2O} E{-}\ddot{N}H_2 + O{=}C(CH_3)_2$$

an imine; acetone

- An amino group of acetoacetate decarboxylase, the enzyme that catalyzes the reaction, forms an imine with acetoacetate.
- The positively charged nitrogen readily accepts the pair of electrons left behind when the substrate loses CO_2.
- Decarboxylation, followed by protonation of the CH_2 group, forms an imine.
- Hydrolysis of the imine produces the decarboxylated product (acetone) and regenerates the enzyme (Section 12.8).

In ketosis, a pathological condition that can occur in people with diabetes, the body produces more acetoacetate than can be metabolized. The excess acetoacetate is decarboxylated, so ketosis can be recognized by the smell of acetone on a person's breath.

13.11 ORGANIZING WHAT WE KNOW ABOUT THE REACTIONS OF ORGANIC COMPOUNDS

We have seen that the families of organic compounds can be put into one of four groups, and that all the members of a group react in similar ways. Now that we have finished studying the families in Group IV, let's revisit this group.

Both families in Group IV have carbonyl groups, and since the carbonyl carbon is an *electrophile*, both families in this group react with *nucleophiles*.

- The first family (carboxylic acids and carboxylic acid derivatives) has a group attached to the carbonyl carbon that can be replaced by another group. Therefore, this family undergoes nucleophilic acyl substitution reactions.
- The second family (aldehyde and ketones) does not have a group attached to the carbonyl carbon that can be replaced by another group. Therefore, this family undergoes nucleophilic addition reactions with strongly basic nucleophiles such as R^- or H^-. If the attacking atom of the nucleophile is an oxygen or a nitrogen and there is enough acid in the solution to protonate the OH group of the tetrahedral compound formed by the nucleophilic addition reaction, then water is eliminated from the addition product.
- Aldehydes, ketones, and esters have a hydrogen on an α-carbon that can be removed by a base. Removal of a hydrogen from an α-carbon creates an enolate ion that can react with electrophiles.

I

R—CH═CH—R
an alkene

R—C≡C—R
an alkyne

R—CH═CH—CH═CH—R
a diene

These are nucleophiles.

They undergo electrophilic addition reactions.

II

Benzene is a nucleophile.

It undergoes electrophilic aromatic substitution reactions.

III

R—X (X = F, Cl, Br, I)
an alkyl halide

R—OH
an alcohol

R—OR
an ether

an epoxide

These are electrophiles.

They undergo nucleophilic substitution and/or elimination reactions.

IV

These are electrophiles.

They undergo nucleophilic acyl substitution reactions or nucleophilic addition reactions.

Removal of a hydrogen from an α-carbon forms a nucleophile that can react with electrophiles.

SOME IMPORTANT THINGS TO REMEMBER

- A hydrogen bonded to an α-carbon of an aldehyde, ketone, or ester is sufficiently acidic to be removed by a strong base.
- Aldehydes and ketones (pK_a ~16 to 20) are more acidic than esters (pK_a ~25). A hydrogen bonded to an α-carbon flanked by two carbonyl groups is even more acidic (pK_a ~9 to 11).
- **Keto–enol interconversion** can be catalyzed by acids or by bases. Generally, the **keto tautomer** is more stable.
- In an **aldol addition,** the enolate ion of an aldehyde or a ketone reacts with the carbonyl carbon of a second molecule of aldehyde or ketone, forming a β-hydroxyaldehyde or a β-hydroxyketone. The new C—C bond forms between the α-carbon of one molecule

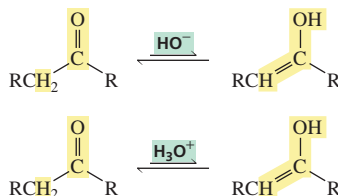
and the carbon that formerly was the carbonyl carbon of the other molecule.

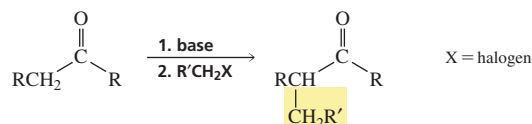
- The product of an aldol addition can be dehydrated under acidic or basic conditions to form an **aldol condensation** product.
- In a **Claisen condensation,** the enolate ion of an ester reacts with a second molecule of ester, eliminating an $^{-}$OR group to form a β-keto ester.
- Carboxylic acids with a carbonyl group at the 3-position **decarboxylate** when they are heated.

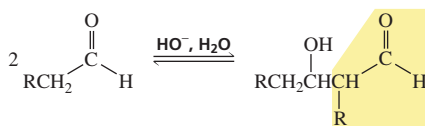
SUMMARY OF REACTIONS

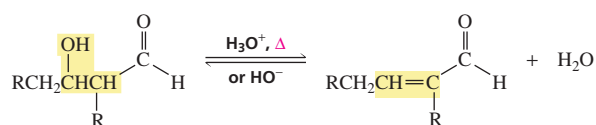
1. Keto–enol interconversion (Section 13.3). The mechanisms are shown on page 493.

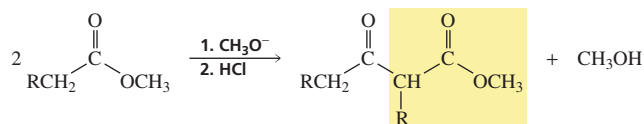
$$RCH_2C(=O)R \underset{}{\overset{HO^-}{\rightleftharpoons}} RCH{=}C(OH)R$$

$$RCH_2C(=O)R \underset{}{\overset{H_3O^+}{\rightleftharpoons}} RCH{=}C(OH)R$$

2. Alkylating the α-carbon of carbonyl compounds (Section 13.4). The mechanism is shown on on page 495.

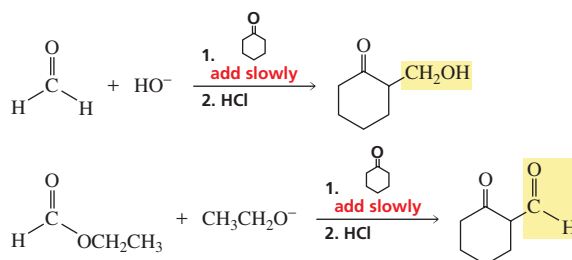
$$RCH_2C(=O)R \xrightarrow[\text{2. } R'CH_2X]{\text{1. base}} RCH(CH_2R')C(=O)R \qquad X = \text{halogen}$$

3. An aldol addition of two aldehydes, two ketones, or an aldehyde and a ketone (Section 13.5). The mechanism is shown on page 497.

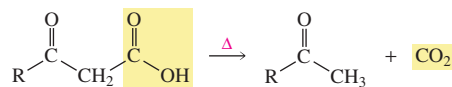
$$2\ RCH_2C(=O)H \overset{HO^-,\ H_2O}{\rightleftharpoons} RCH_2CH(OH)CH(R)C(=O)H$$

4. An aldol condensation is an aldol addition followed by acid-catalyzed or base-catalyzed dehydration (Section 13.6). The mechanism for base-catalyzed dehydration is shown on page 498.

$$RCH_2CH(OH)CH(R)C(=O)H \underset{\text{or } HO^-}{\overset{H_3O^+,\ \Delta}{\rightleftharpoons}} RCH_2CH{=}C(R)C(=O)H + H_2O$$

5. A Claisen condensation of two esters (Section 13.8). The mechanism is shown on page 501.

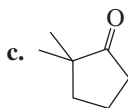
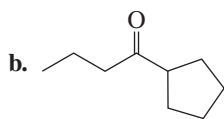
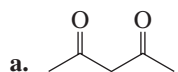
$$2\ RCH_2C(=O)OCH_3 \xrightarrow[\text{2. HCl}]{\text{1. } CH_3O^-} RCH_2C(=O)CH(R)C(=O)OCH_3 + CH_3OH$$

6. Crossed addition and condensation reactions when one of the carbonyl compounds does not have any α-hydrogens (Sections 13.7 and 13.8).

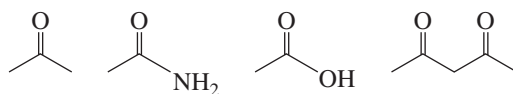
$$HC(=O)H + HO^- \xrightarrow[\text{2. HCl}]{\text{1. cyclohexanone, add slowly}} \text{2-(hydroxymethyl)cyclohexanone } (CH_2OH)$$

$$HC(=O)OCH_2CH_3 + CH_3CH_2O^- \xrightarrow[\text{2. HCl}]{\text{1. cyclohexanone, add slowly}} \text{2-formylcyclohexanone } (C(=O)H)$$

7. Decarboxylation of 3-oxocarboxylic acids (Section 13.9). The mechanism is shown on page 503.

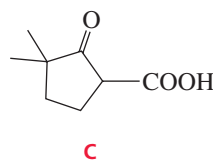
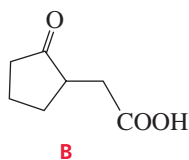
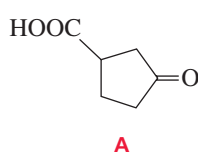
$$RC(=O)CH_2C(=O)OH \xrightarrow{\Delta} RC(=O)CH_3 + CO_2$$

PROBLEMS

24. Draw the enol tautomers for each of the following compounds. If the compound has more than one enol tautomer, indicate which one is more stable.

a. **b.** **c.**

25. Number the following compounds in order from strongest acid to weakest acid.

NH$_2$ OH

26. Explain why the α-hydrogen of an *N,N*-disubstituted amide is less acidic (pK_a = 30) than the α-hydrogen of an ester (pK_a = 25).

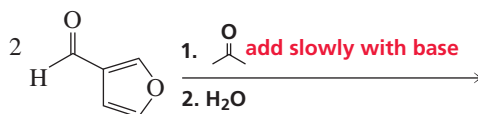
27. Explain why the pK_a of a hydrogen bonded to the sp^3 carbon of propene is greater (pK_a = 42) than that of any of the carbon acids listed in Table 13.1, but is less than the pK_a of an alkane (pK_a > 60).

28. Which of the following compounds decarboxylates when heated?

29. What aldehyde or ketone would be obtained when each of the following compounds is heated in a basic aqueous solution?

a. 4-hydroxy-4-methyl-2-pentanone **b.** 2,4-dicyclohexyl-3-hydroxybutanal

30. Draw the structures of the four β-keto esters that would be obtained from a mixture of ethyl formate and ethyl butanoate in a solution of $NaOCH_3$ in methanol.

31. What is the product of the following reaction?

2 (furan-3-carbaldehyde) → 1. (acetone) add slowly with base; 2. H_2O

32. Arachidic acid is a saturated 20-carbon fatty acid. How many moles of malonyl-CoA are required for the synthesis of one mole of arachidic acid?

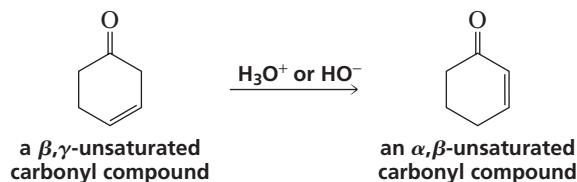
33. a. If the biosynthesis of arachidic acid were carried out with CD_3COSR and nondeuterated malonyl thioester, how many deuteriums would be incorporated into arachidic acid?

b. If the biosynthesis of arachidic acid were carried out with $^-OOCCD_2COSR$ and nondeuterated acetyl thioester, how many deuteriums would be incorporated into arachidic acid?

34. Using cycloheptanone as the reactant, show the product of
a. acid-catalyzed keto–enol interconversion. **b.** an aldol addition. **c.** an aldol condensation.

35. A β,γ-unsaturated carbonyl compound rearranges to a more stable conjugated α,β-unsaturated compound in the presence of either acid or base.
a. Propose a mechanism for the base-catalyzed rearrangement. **b.** Propose a mechanism for the acid-catalyzed rearrangement.

a β,γ-unsaturated carbonyl compound

an α,β-unsaturated carbonyl compound

36. Draw the structures of the four β-hydroxyaldehydes that would be obtained from a mixture of butanal and pentanal in a basic aqueous solution.

37. Explain why a racemic mixture is formed when (*R*)-4-methyl-3-hexanone is dissolved in an acidic or basic solution.

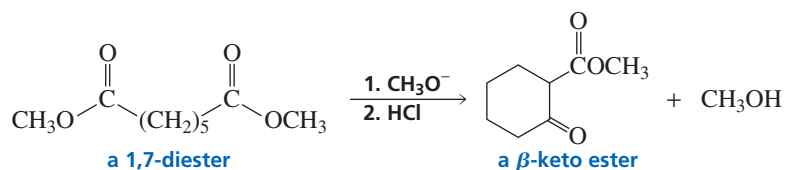
38. Give an example of a ketone other than the one in Problem 37 that would undergo acid- or base-catalyzed racemization.

39. Both 2,6-heptanedione and 2,8-nonanedione form a product with a six-membered ring when treated with sodium hydroxide. Draw the structures of the six-membered ring products.

40. What is the product of the reaction of 2,8-nonanedione and aqueous sodium hydroxide?

41. Draw the mechanism for the following reaction:

$CH_3O-C(=O)-(CH_2)_5-C(=O)-OCH_3$ $\xrightarrow{\text{1. } CH_3O^- \text{ 2. HCl}}$ (cyclohexanone with $COCH_3$ ester) + CH_3OH

a 1,7-diester a β-keto ester

42. What product is formed when a 1,8-diester instead of a 1,7-diester undergoes the previous reaction?

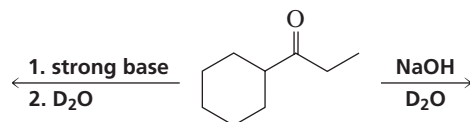
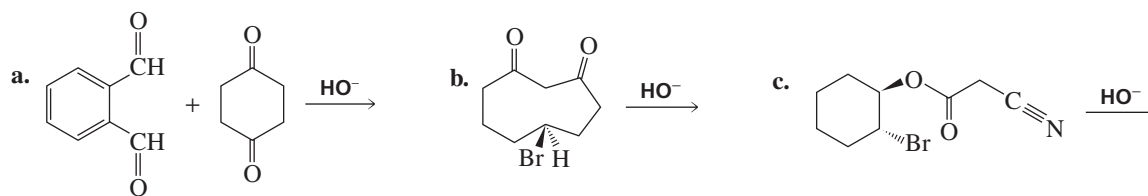
43. Draw the products of the following reactions:

1. strong base 2. D_2O ← (1-cyclohexyl-1-butanone) → NaOH, D_2O

44. Draw the products of the following reactions:

a. (phthalaldehyde, CH=O, CH=O) + (1,4-cyclohexanedione) $\xrightarrow{HO^-}$

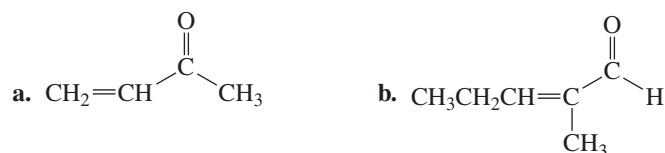
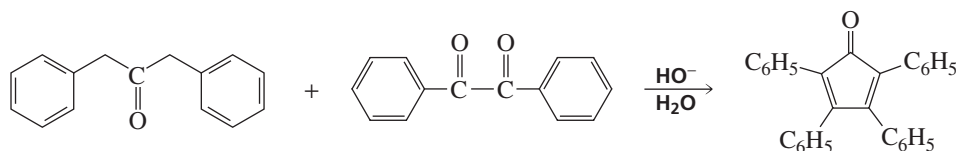
b. (cyclodecanedione with Br, H) $\xrightarrow{HO^-}$

c. (cyclohexyl ester of cyanoacetic acid with Br, $C\equiv N$) $\xrightarrow{HO^-}$

45. Describe how the following compounds can be synthesized using reagents that contain no more than three carbons:

a. $CH_2{=}CH-C(=O)-CH_3$

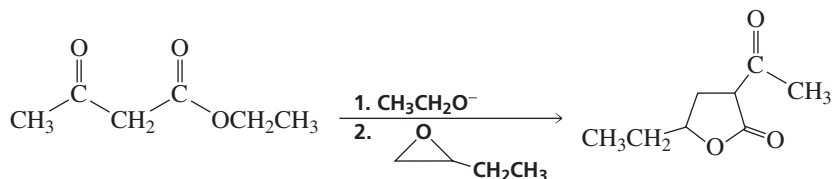
b. $CH_3CH_2CH{=}C(CH_3)-C(=O)-H$

46. Propose a mechanism for the following reaction:

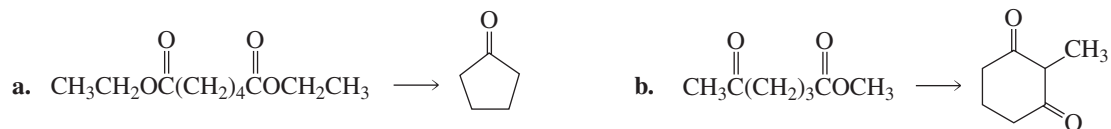
$C_6H_5CH_2-C(=O)-CH_2C_6H_5$ + $C_6H_5-C(=O)-C(=O)-C_6H_5$ $\xrightarrow{HO^-,\ H_2O}$ (tetraphenylcyclopentadienone: C_6H_5, C_6H_5, C_6H_5, C_6H_5)

47. Which would require a higher temperature: decarboxylation of a β-dicarboxylic acid or decarboxylation of a β-keto acid?

48. When the enzymatic decarboxylation of acetoacetate is carried out in $H_2{}^{18}O$, all the acetone that is formed contains ^{18}O. What does this tell you about the mechanism of the reaction?

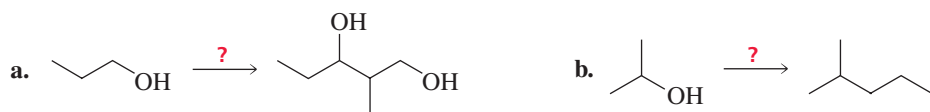
49. Propose a mechanism for the following reaction:

$CH_3C(=O)CH_2C(=O)OCH_2CH_3$ → (1. $CH_3CH_2O^-$; 2. epoxide with CH_2CH_3) → lactone product with $C(=O)CH_3$ and CH_3CH_2 substituents

50. Show how the following compounds could be synthesized from the given starting materials:

a. $CH_3CH_2OC(=O)(CH_2)_4C(=O)OCH_2CH_3$ ⟶ cyclopentanone

b. $CH_3C(=O)(CH_2)_3C(=O)OCH_3$ ⟶ 2-acetylcyclohexanone (CH_3, O)

51. Show how the following compounds could be synthesized. The only carbon-containing compound available to you for each synthesis is shown.

a. OH $\xrightarrow{?}$ OH, OH

b. OH $\xrightarrow{?}$

52. a. Draw the enol tautomer of 2,4-pentanedione.

b. Most ketones form less than 1% enol in an aqueous solution. Explain why the enol tautomer of 2,4-pentanedione is much more prevalent (15%).

14 Radicals

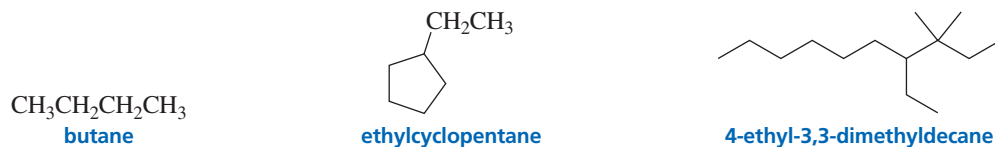
The world needs a renewable, nonpolluting, and economically affordable source of energy (see page 514).

Alkanes are widespread both on Earth and on other planets. The atmospheres of Jupiter, Saturn, Uranus, and Neptune contain large quantities of methane (CH_4), the smallest alkane, which is an odorless and flammable gas. The blue colors of Uranus and Neptune are the result of methane in their atmospheres. Alkanes on Earth are found in natural gas and petroleum, which are formed by the decomposition of plant and animal materials that have been buried for long periods of time in the Earth's crust, where oxygen is scarce. As a result, natural gas and petroleum are known as fossil fuels.

We have seen that there are three classes of hydrocarbons: *alkanes,* which contain only carbon—carbon single bonds; *alkenes,* which contain carbon–carbon double bonds; and *alkynes,* which contain carbon–carbon triple bonds. Because **alkanes** do not contain any double or triple bonds, they are called **saturated hydrocarbons,** meaning they are saturated with hydrogen. A few examples of alkanes are shown here.

$CH_3CH_2CH_2CH_3$
butane

CH_2CH_3
ethylcyclopentane

4-ethyl-3,3-dimethyldecane

14.1 ALKANES ARE UNREACTIVE COMPOUNDS

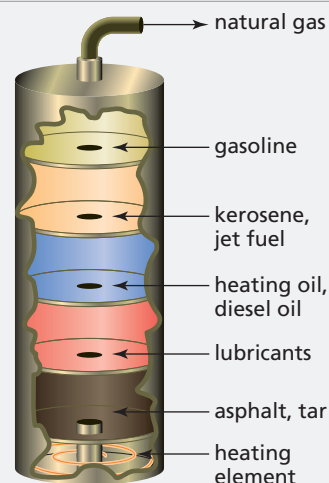
We have seen that the carbon–carbon double and triple bonds of *alkenes* and *alkynes* are composed of strong σ bonds and weaker π bonds and that, because of their relatively weak π bonds, alkenes and alkynes undergo electrophilic addition reactions (Sections 6.0 and 6.13).

Alkanes have only strong σ bonds. In addition, the electrons in the C—C and C—H σ bonds are shared equally or almost equally by the bonding atoms, so none of the atoms in an alkane has any significant charge. This means that alkanes are neither nucleophiles nor electrophiles, so neither electrophiles nor nucleophiles are attracted to them. Alkanes, therefore, are relatively unreactive compounds. The failure of alkanes to undergo reactions prompted early organic chemists to call them *paraffins,* from the Latin *parum affinis,* which means "little affinity" (for other compounds).

Natural Gas and Petroleum

Natural gas is approximately 75% methane. The remaining 25% is composed of other small alkanes, such as ethane, propane, and butane. In the 1950s, natural gas replaced coal as the main energy source for domestic and industrial heating in many parts of the United States.

Petroleum is a complex mixture of alkanes and cycloalkanes that can be separated into fractions by distillation. Natural gas is the fraction that boils off at the lowest temperature (hydrocarbons containing fewer than 5 carbons). The fraction that boils at somewhat higher temperatures (hydrocarbons containing 5–11 carbons) is gasoline; the next fraction (9–16 carbons) includes kerosene and jet fuel. The fraction with 15 to 25 carbons is used for heating oil and diesel oil, and the highest boiling fraction is used for lubricants and greases. After distillation, a nonvolatile residue called asphalt or tar is left behind.

The 5- to 11-carbon fraction that is used for gasoline is actually a poor fuel for internal combustion engines. To become a high-performance gasoline, it requires a process known as catalytic cracking. Catalytic cracking converts straight-chain hydrocarbons that are poor fuels into branched-chain compounds that are high-performance fuels (Section 3.2). Originally, cracking (also called pyrolysis) required heating the gasoline to very high temperatures in order to obtain hydrocarbons with three to five carbons. Modern cracking methods use catalysts to accomplish the same thing at much lower temperatures.

Fossil Fuels: A Problematic Energy Source

Modern society faces three major problems as a consequence of our dependence on fossil fuels for energy. First, these fuels are a nonrenewable resource and the world's supply is continually decreasing. Second, a group of Middle Eastern and South American countries controls a large portion of the world's supply of petroleum. These countries have formed a cartel called the *Organization of Petroleum Exporting Countries* (*OPEC*) that controls both the supply and the price of crude oil. Political instability in any OPEC country can seriously affect the world's oil supply.

Third, burning fossil fuels—particularly coal—increases the concentration of CO_2 in the atmosphere; burning coal also increases the concentration of atmospheric SO_2. Scientists have established experimentally that SO_2 causes "acid rain," a threat to plants and, therefore, to our food and oxygen supplies (see page 68 and Section 2.2).

The concentration of atmospheric CO_2 at Mauna Loa, Hawaii, has been periodically measured since 1958. The concentration has increased 25% since the first measurements were taken, causing scientists to predict an increase in the Earth's temperature as a result of the absorption of infrared radiation by CO_2 (the *greenhouse effect*). A steady increase in the temperature of the Earth would have devastating consequences, including the formation of new deserts, massive crop failure, and the melting of glaciers with a concomitant rise in sea level. Clearly, what we need is a renewable, nonpolitical, nonpolluting, and economically affordable source of energy.

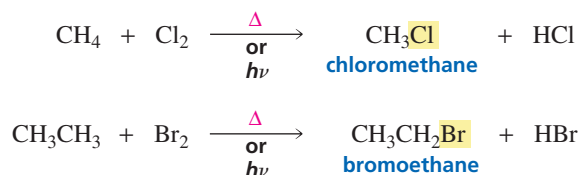
14.2 THE CHLORINATION AND BROMINATION OF ALKANES

Alkanes react with chlorine (Cl_2) or bromine (Br_2) to form alkyl chlorides or alkyl bromides. These **halogenation reactions** take place only at high temperatures or in the presence of light. (Irradiation with light is symbolized by *hν*.)

$$CH_4 + Cl_2 \xrightarrow[h\nu]{\Delta \text{ or}} CH_3Cl + HCl$$

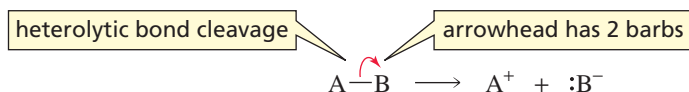
chloromethane

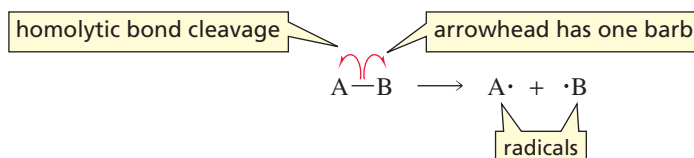
$$CH_3CH_3 + Br_2 \xrightarrow[h\nu]{\Delta \text{ or}} CH_3CH_2Br + HBr$$

bromoethane

The relative reactivities of the halogens with an alkane are $F_2 > Cl_2 > Br_2 > I_2$. F_2 is so reactive that it reacts explosively with alkanes, and I_2 is so unreactive that the halogenation reaction cannot occur. Therefore, halogenation reactions with Cl_2 or Br_2 are the only productive reactions that alkanes undergo.

When a bond breaks so that both of its electrons stay with one of the atoms, the process is called **heterolytic bond cleavage** or **heterolysis.**

heterolytic bond cleavage — arrowhead has 2 barbs

$$A{-}B \longrightarrow A^+ + :B^-$$

An arrowhead with two barbs signifies the movement of two electrons.

When a bond breaks so that each of the atoms retains one of the bonding electrons, the process is called **homolytic bond cleavage** or **homolysis.** Homolysis results in the formation of radicals. A **radical** (often called a **free radical**) is a species containing an atom with an unpaired electron. A radical is highly reactive because acquiring an electron will complete its octet.

An arrowhead with one barb—sometimes called a fishhook—signifies the movement of one electron.

The mechanism for the halogenation of an alkane is well understood. As an example, let's look at the mechanism for the monochlorination of methane. The monochlorination of alkanes other than methane has the same mechanism.

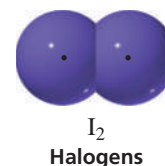
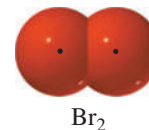
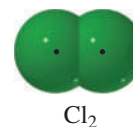
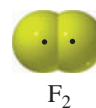
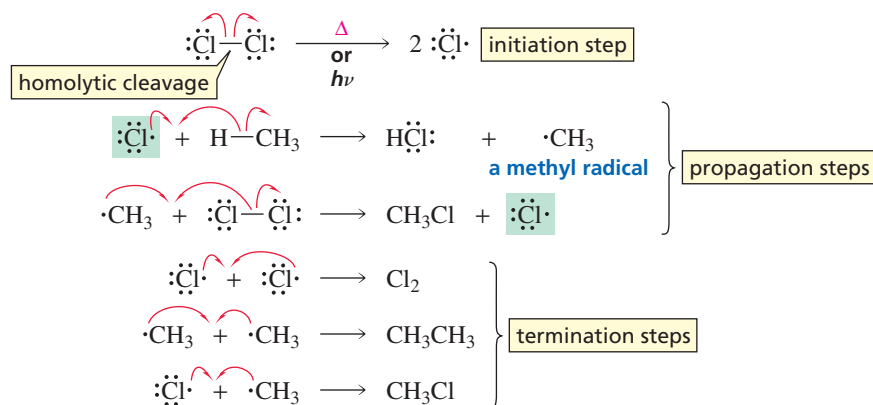
MECHANISM FOR THE MONOCHLORINATION OF METHANE

F_2

Cl_2

Br_2

I_2

Halogens

- Heat or light supplies the energy required to break the Cl—Cl bond homolytically. This is the **initiation step** of the reaction because it creates radicals from a molecule in which all the electrons are paired.
- The chlorine radical formed in the initiation step removes a hydrogen atom from the alkane (in this case methane), forming HCl and a methyl radical.
- The methyl radical removes a chlorine atom from Cl_2, forming chloromethane and another chlorine radical, which can then remove a hydrogen atom from another molecule of methane.

  Steps 2 and 3 are **propagation steps** because *the radical created in the first propagation step reacts in the second propagation step to produce the radical that participates in the first propagation step.* Thus, the two propagation steps are repeated over and over. A propagation step is one that propagates the chain. The first propagation step is the rate-determining step of the overall reaction.

Radical chain reactions have initiation, propagation, and termination steps.

- Any two radicals in the reaction mixture can combine to form a molecule in which all the electrons are paired. The combination of two radicals is called a **termination step** because it helps bring the reaction to an end by decreasing the number of radicals available to propagate the reaction. Any two radicals can combine, so a radical reaction produces a mixture of products.

Because the reaction has radical intermediates and repeating propagation steps, it is called a **radical chain reaction.** This particular radical chain reaction is called a **radical substitution** reaction because it substitutes a chlorine for one of the hydrogens of the alkane.

The bromination of alkanes has the same mechanism as the chlorination of alkanes.

Why Radicals No Longer Have to Be Called Free Radicals

At one time an "R" group was called a radical. For example, the OH substituent in CH_3CH_2OH was said to be attached to an ethyl radical. To distinguish this kind of ethyl radical from $CH_3\dot{C}H_2$, which has an unpaired electron and is not attached to a substituent, $CH_3\dot{C}H_2$ was called a "free radical"—it was free from attachment to a substituent. Now that we call "R" a *substituent* or a *group* instead of a *radical,* we no longer need to call a compound with an unpaired electron a "free radical"; the word *radical* is now unambiguous.

PROBLEM 1

Write the mechanism for the monobromination of ethane.

PROBLEM 2

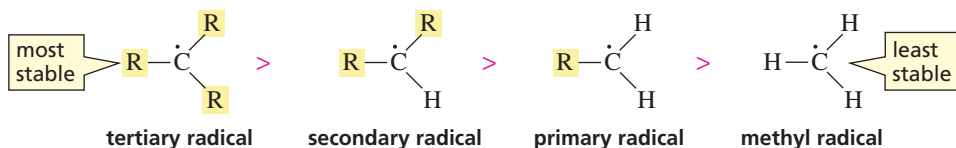
Write the initiation, propagation, and termination steps for the monochlorination of cyclohexane.

14.3 RADICAL STABILITY DEPENDS ON THE NUMBER OF ALKYL GROUPS ATTACHED TO THE CARBON WITH THE UNPAIRED ELECTRON

Radicals are classified according to the carbon that bears the unpaired electron. **Primary radicals** have the unshared electron on a primary carbon, **secondary radicals** have the unshared electron on a secondary carbon, and **tertiary radicals** have the unshared electron on a tertiary carbon.

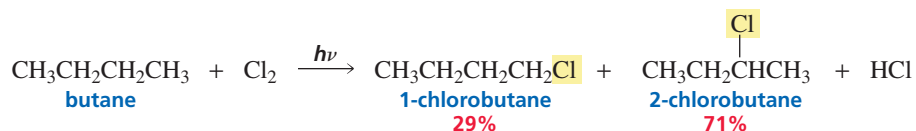
The relative stabilities of primary, secondary, and tertiary alkyl radicals follow the same order as the relative stabilities of primary, secondary, and tertiary carbocations (Section 6.2).

relative stabilities of alkyl radicals

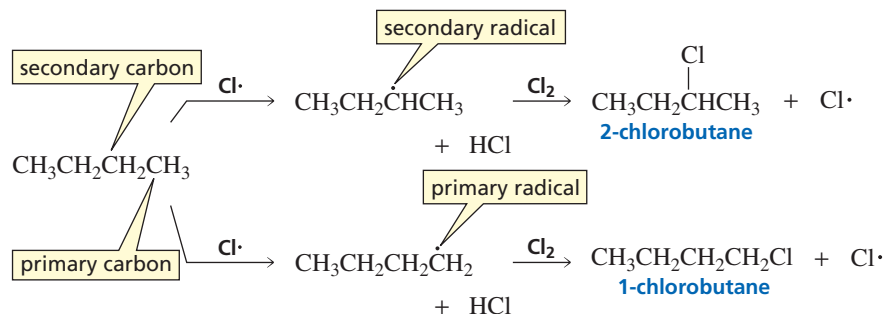
most stable $R_3C\cdot$ (tertiary radical) > $R_2CH\cdot$ (secondary radical) > $RCH_2\cdot$ (primary radical) > $H_3C\cdot$ (methyl radical) least stable

Stability of alkyl radicals: 3° > 2° > 1°

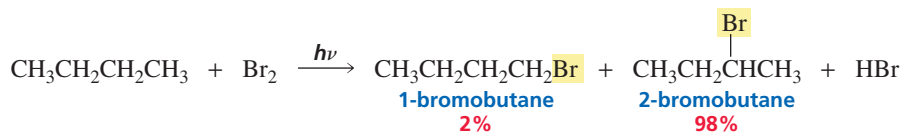
14.4 THE DISTRIBUTION OF PRODUCTS DEPENDS ON RADICAL STABILITY

Two different alkyl halides are obtained from the monochlorination of butane. Substitution of a hydrogen bonded to one of the primary carbons produces 1-chlorobutane, whereas substitution of a hydrogen bonded to one of the secondary carbons forms 2-chlorobutane.

$$\underset{\text{butane}}{CH_3CH_2CH_2CH_3} + Cl_2 \xrightarrow{h\nu} \underset{\substack{\text{1-chlorobutane}\\ 29\%}}{CH_3CH_2CH_2CH_2Cl} + \underset{\substack{\text{2-chlorobutane}\\ 71\%}}{CH_3CH_2CH(Cl)CH_3} + HCl$$

The rate-determining step of halogenation of an alkane is the first propagation step—removal of a hydrogen atom from the alkane. It is easier for a chlorine radical to remove a hydrogen atom from a secondary carbon to form a secondary radical than from a primary carbon to form a primary radical; the secondary radical is more stable, so it is formed more rapidly. As a result, 2-chlorobutane is the major product of the reaction.

$$CH_3CH_2CH_2CH_3 \text{ (secondary carbon)} \xrightarrow{Cl\cdot} \underset{\text{secondary radical}}{CH_3CH_2\dot{C}HCH_3} + HCl \xrightarrow{Cl_2} \underset{\text{2-chlorobutane}}{CH_3CH_2CH(Cl)CH_3} + Cl\cdot$$

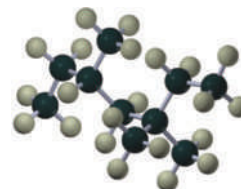
$$CH_3CH_2CH_2CH_3 \text{ (primary carbon)} \xrightarrow{Cl\cdot} \underset{\text{primary radical}}{CH_3CH_2CH_2\dot{C}H_2} + HCl \xrightarrow{Cl_2} \underset{\text{1-chlorobutane}}{CH_3CH_2CH_2CH_2Cl} + Cl\cdot$$

A bromine radical is less reactive than a chlorine radical. Therefore, the bromine radical has a greater preference for the secondary hydrogen because the secondary radical is easier to form. As a result, more of the secondary alkyl halide is formed when the alkane is brominated than when it is chlorinated.

$$CH_3CH_2CH_2CH_3 + Br_2 \xrightarrow{h\nu} \underset{\substack{\text{1-bromobutane}\\ 2\%}}{CH_3CH_2CH_2CH_2Br} + \underset{\substack{\text{2-bromobutane}\\ 98\%}}{CH_3CH_2CH(Br)CH_3} + HBr$$

A bromine radical is less reactive and more selective than a chlorine radical.

PROBLEM 3

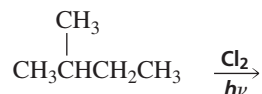
How many hydrogens are attached to secondary carbons in the structure in the margin?

PROBLEM 4

Which of the hydrogens in the structure in the margin is the easiest for a chlorine radical to remove?

PROBLEM-SOLVING STRATEGY

Determining the Number of Monohalogenation Products

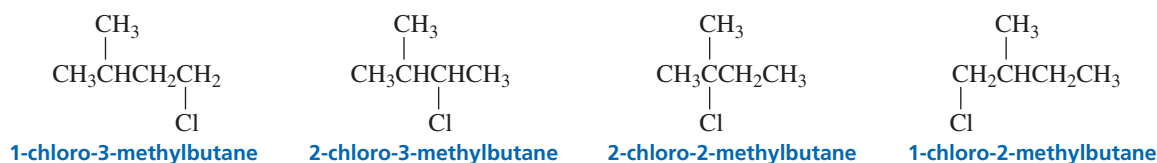
How many monochlorination products would be obtained from the following reaction? Disregard stereoisomers.

$$\underset{\displaystyle CH_3CHCH_2CH_3}{\overset{\displaystyle CH_3}{|}} \xrightarrow[h\nu]{Cl_2}$$

Replace each different hydrogen with a chlorine. Replacing one of the three hydrogens of the methyl group on the right side of the molecule will form 1-chloro-3-methylbutane; replacing one of the secondary hydrogens will form 2-chloro-3-methylbutane; replacing the tertiary hydrogen will form 2-chloro-2-methylbutane, and replacing any of the six hydrogens of the two methyl groups on the left side of the molecule will form 1-chloro-2-methylbutane. Thus, four products will be formed.

$CH_3CH(CH_3)CH_2CH_2Cl$ — 1-chloro-3-methylbutane

$CH_3CH(CH_3)CHClCH_3$ — 2-chloro-3-methylbutane

$CH_3CCl(CH_3)CH_2CH_3$ — 2-chloro-2-methylbutane

$ClCH_2CH(CH_3)CH_2CH_3$ — 1-chloro-2-methylbutane

To see that replacing a hydrogen on either of the methyl groups on the left side of the molecule leads to the same compound, replace a hydrogen on each methyl group and then name the compounds. If the compounds have the same name, they are the same compound.

$Cl—CH_2CH(CH_3)CH_2CH_3$ — 1-chloro-2-methylbutane

$CH_3CH(CH_2—Cl)CH_2CH_3$ — 1-chloro-2-methylbutane

Now use the strategy you have just learned to solve Problem 5.

PROBLEM 5♦

How many alkyl chlorides can be obtained from monochlorination of the following alkanes? Disregard stereoisomers.

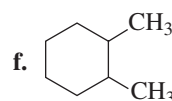
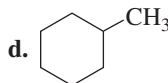
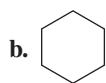
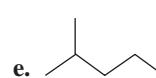
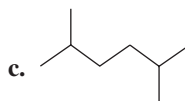
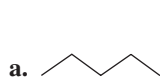
a. (skeletal structure: butane)

b. (cyclohexane)

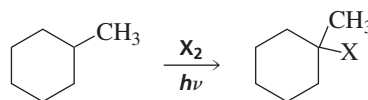
c. (skeletal structure: 2,4-dimethylpentane)

d. (methylcyclohexane, CH_3)

e. (skeletal structure: 2-methylbutane)

f. (1,2-dimethylcyclohexane, CH_3, CH_3)

PROBLEM 6 Solved

Would chlorination or bromination of methylcyclohexane produce a greater yield of 1-halo-1-methylcyclohexane?

$$\text{methylcyclohexane }(CH_3) \xrightarrow[h\nu]{X_2} \text{1-halo-1-methylcyclohexane }(CH_3, X)$$

Solution The desired product is a tertiary alkyl halide, so the question becomes, "Will bromination or chlorination produce a greater yield of a tertiary alkyl halide?" Because a bromine radical is less reactive, it is more selective. Therefore, it has a greater preference for the tertiary hydrogen because the tertiary radical is easier to form. Therefore, bromination will produce a greater yield of the desired compound. Chlorination will form some of the tertiary alkyl halide, but it will also form significant amounts of primary and secondary alkyl halides.

PROBLEM 7♦

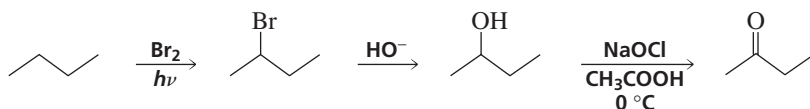
Would chlorination or bromination produce a greater yield of 1-halo-2,3-dimethylbutane?

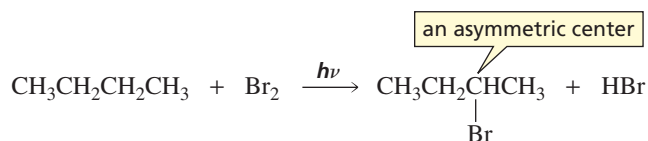
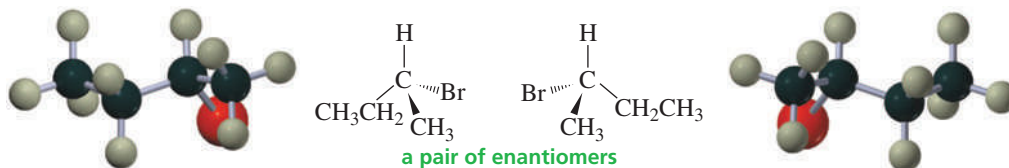
PROBLEM 8 Solved

How could butanone be prepared from butane?

butane $\xrightarrow{?}$ butanone

Solution We know that the first reaction has to be a radical halogenation because that is the only reaction that an alkane undergoes. Bromination is used rather than chlorination, because a bromine radical is more selective for the secondary hydrogen. A nucleophilic substitution reaction forms the alcohol, which forms the target molecule when it is oxidized.

butane $\xrightarrow[h\nu]{Br_2}$ 2-bromobutane $\xrightarrow{HO^-}$ 2-butanol $\xrightarrow[CH_3COOH,\ 0\ °C]{NaOCl}$ butanone

14.5 THE STEREOCHEMISTRY OF RADICAL SUBSTITUTION REACTIONS

We have seen that when a reactant that does not have an asymmetric center undergoes a reaction that forms a product with one asymmetric center, the product will be a racemic mixture (Section 6.6). Thus, the following *radical substitution reaction* forms a racemic mixture (that is, an equal amount of each enantiomer).

When a reactant that does not have an asymmetric center undergoes a reaction that forms a product with one asymmetric center, the product will be a racemic mixture.

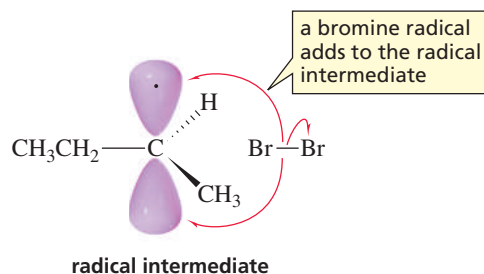
$$CH_3CH_2CH_2CH_3 + Br_2 \xrightarrow{h\nu} CH_3CH_2\underset{Br}{\underset{|}{C}}HCH_3 + HBr$$

(an asymmetric center)

configuration of the products

a pair of enantiomers

The radical substitution reaction forms a racemic mixture because the carbon that bears the unpaired electron in the radical intermediate is sp^2 hybridized, so the three atoms to which it is bonded lie in a plane (Section 1.10). Therefore, the incoming bromine atom has equal access to both sides of the plane. Consequently, identical amounts of the *R* and *S* enantiomers are formed.

radical intermediate

PROBLEM 9

How many products would the reaction in the Problem-Solving Strategy on page 518 form if stereoisomers were included?

14.6 FORMATION OF EXPLOSIVE PEROXIDES

Ethers are a laboratory hazard because they form explosive peroxides by reacting with O_2 when they are exposed to air.

MECHANISM FOR PEROXIDE FORMATION

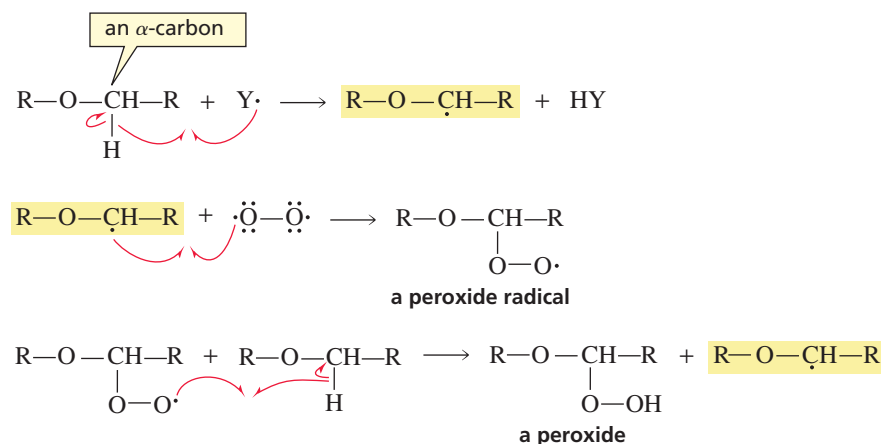
an α-carbon

R—O—CH(H)—R + Y· ⟶ R—O—ĊH—R + HY

R—O—ĊH—R + ·Ö—Ö· ⟶ R—O—CH(O—O·)—R

a peroxide radical

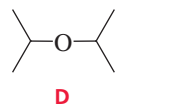
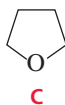
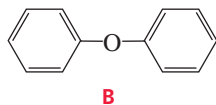
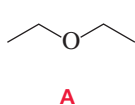
R—O—CH(O—O·)—R + R—O—CH(H)—R ⟶ R—O—CH(O—OH)—R + R—O—ĊH—R

a peroxide

- A chain-initiating radical removes a hydrogen atom from an α-carbon of the ether. (The α-carbon is the carbon attached to the oxygen.) This is an initiation step because it creates the radical that is used in the first propagation step.
- The radical formed in the initiation step reacts with oxygen in a propagation step, forming a peroxide radical.
- In the second propagation step, the peroxide radical removes a hydrogen atom from the α-carbon of another molecule of ether to form a peroxide and regenerate the radical used in the first propagation step.

A **peroxide** is a compound with an O—O bond. Because an O—O bond is easily cleaved homolytically, a peroxide forms radicals that then can create new radicals—it is a **radical initiator.** Thus, the peroxide product of the preceding radical chain reaction can initiate another radical chain reaction—an explosive situation. To prevent the formation of explosive peroxides, ethers contain a stabilizer that traps the chain-initiating radical. Once an ether is purified (in which case it no longer contains the stabilizer), it has to be used or discarded within 24 hours.

PROBLEM 10♦

a. Which ether is most apt to form a peroxide? **b.** Which ether is least apt to form a peroxide?

A B C D

14.7 RADICAL REACTIONS OCCUR IN BIOLOGICAL SYSTEMS

Because of the large amount of heat or light energy required to initiate a radical reaction and the difficulty in controlling a chain reaction once it is initiated, scientists assumed for a long time that radical reactions were not important in biological systems. It is now widely recognized, however, that many biological reactions involve radicals. The radicals in these reactions, instead of being generated by heat or light, are formed by the interaction of organic molecules with metal ions. The radical reactions take place at the active sites of enzymes (Section 5.11). Containing the chain reaction at a specific site allows the reaction to be controlled.

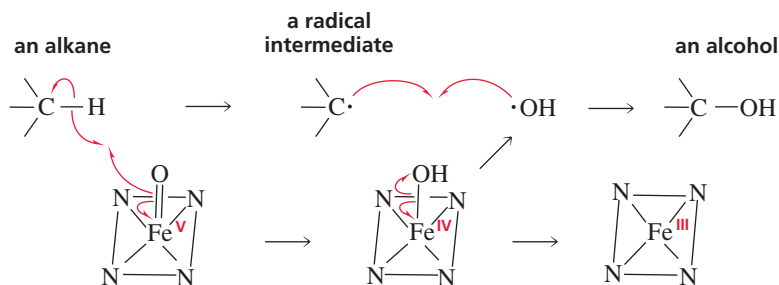
Water-soluble (polar) compounds are readily eliminated by the body. In contrast, water-insoluble (nonpolar) compounds are not readily eliminated but, instead, accumulate in the nonpolar components of cells. For cells to avoid becoming "toxic dumps," nonpolar compounds that are ingested (such as drugs, foods, and environmental pollutants) must be converted into polar compounds that can be excreted.

A radical reaction carried out in the liver converts nonpolar hydrocarbons into less toxic polar alcohols by substituting an H in the hydrocarbon with an OH. The reaction is catalyzed by an iron-containing enzyme.

A radical intermediate is created when $Fe^{V}{=}O$ removes a hydrogen atom from the alkane. Then Fe^{IV}—OH dissociates homolytically into Fe^{III} and ·OH, and the ·OH immediately combines with the radical intermediate to form the alcohol.

an alkane a radical intermediate an alcohol

—C—H ⟶ —C· ·OH ⟶ —C—OH

Fe^{V} ⟶ Fe^{IV} ⟶ Fe^{III}

This reaction can also have the opposite toxicological effect. For example, studies found that when animals inhale dichloromethane (CH_2Cl_2), it becomes a carcinogen as a result of an H being substituted by an OH.

Fats and oils are easily oxidized by O_2 by means of a radical chain reaction to form compounds that have strong odors. These compounds are responsible for the unpleasant taste and smell associated with sour milk and rancid butter.

Decaffeinated Coffee and the Cancer Scare

Animal studies revealing that dichloromethane becomes a carcinogen when inhaled immediately led to a study of thousands of workers who inhaled dichloromethane daily. However, no increased risk of cancer was found in this group. (This shows that the results of studies done on humans do not always agree with the results of those done on laboratory animals.)

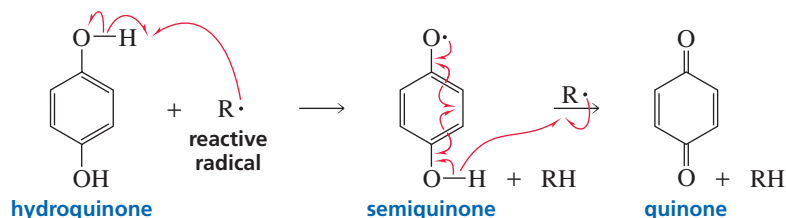
Because dichloromethane was the solvent used to extract caffeine from coffee beans in the manufacture of decaffeinated coffee, a study was done to see what happened to animals that drank dichloromethane. When dichloromethane was added to the drinking water given to laboratory rats and mice, researchers found no toxic effects, even in rats that had consumed an amount of dichloromethane equivalent to the amount that would be ingested by drinking 120,000 cups of decaffeinated coffee per day and in mice that had consumed an amount equivalent to drinking 4.4 million cups of decaffeinated coffee per day.

However, because of the initial concern, researchers sought alternative methods for extracting caffeine from coffee beans. Extraction by CO_2 at supercritical temperatures and pressures was found to be a better method, because it extracts caffeine without simultaneously extracting some of the flavor compounds, as dichloromethane does. This was one of the first green (environmentally benign) commercial chemical processes to be developed. After the caffeine has been removed, the CO_2 can be recycled, whereas dichloromethane is not a substance that should be released into the environment (Section 6.0).

Cell membranes have structures similar to those of fats and oils (page 125 and Section 20.2. Therefore, they undergo the same radical reactions that fats and oils undergo that lead to degradation. Radical reactions in cells have been implicated in the aging process.

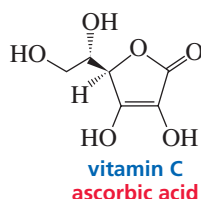
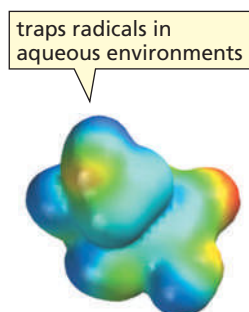
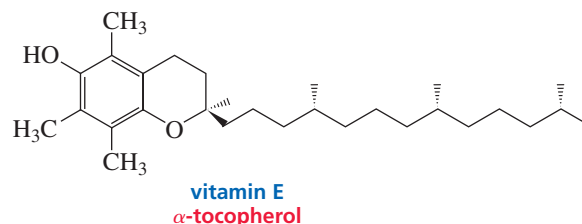
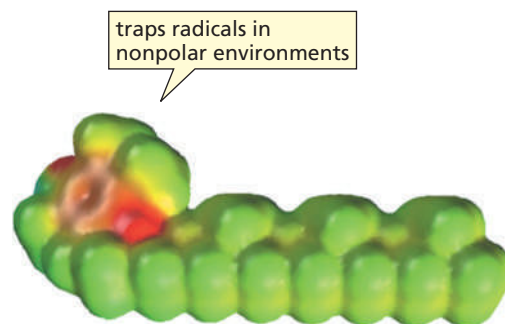
Because radicals are implicated in the aging process, many products are available that contain antioxidants.

Clearly, unwanted radicals in cells must be destroyed before they damage cells. Radical reactions can be prevented by **radical inhibitors,** compounds that destroy reactive radicals by converting them into compounds with only paired electrons (or into less reactive radicals). Radical inhibitors are *antioxidants*—that is, they prevent the oxidation reactions caused by radicals.

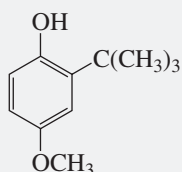
Hydroquinone is an example of a radical inhibitor. When hydroquinone traps a radical by giving it a hydrogen atom with which to pair its electron, it forms semiquinone. Semiquinone can trap another radical and form quinone, a compound whose electrons are all paired. Hydroquinones are found in the cells of all aerobic organisms.

Two other examples of radical inhibitors in living systems are vitamins C and E. Vitamin C (also called ascorbic acid; see Section 16.6) is a water-soluble compound that traps radicals formed in the interior of cells and in blood plasma (both of which have aqueous environments).

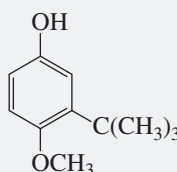
Vitamin E (also called α-tocopherol) is a fat-soluble compound that traps radicals formed in cell membranes, which are nonpolar. Vitamin E is the primary antioxidant for fat tissue in humans and is, therefore, important in preventing the development of atherosclerosis.

Nuts are a natural source of vitamin E.

Why one vitamin functions in aqueous environments and the other in nonaqueous environments is apparent from their structures and their electrostatic potential maps; both show that vitamin C is a relatively polar compound and vitamin E is a nonpolar compound.

Food Preservatives

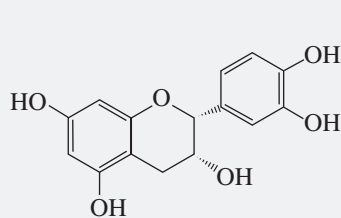
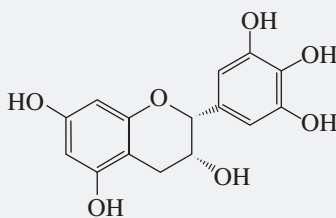
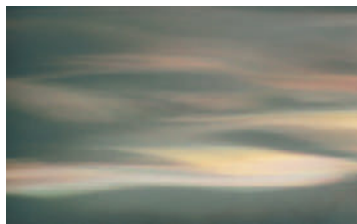
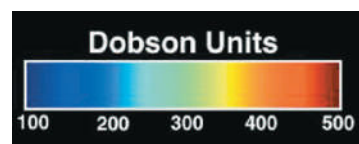
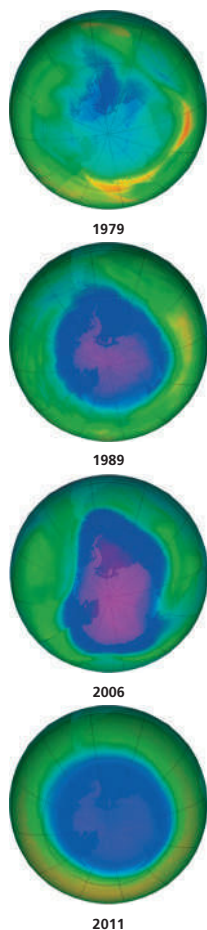
Radical inhibitors found in food are known as *preservatives*. They preserve food by preventing radical chain reactions. Vitamin E is a naturally occurring preservative found in such things as vegetable oil, sunflower seeds, and spinach. BHA and BHT are synthetic preservatives that are added to many packaged foods. Notice that, like hydroquinone, vitamin E and all the synthetic preservatives are phenols.

OH, $C(CH_3)_3$, OCH_3 — OH, $C(CH_3)_3$, OCH_3

butylated hydroxyanisole
BHA

OH, $(CH_3)_3C$, $C(CH_3)_3$, CH_3

butylated hydroxytoluene
BHT

food preservatives

Is Chocolate a Health Food?

We have long been told that our diets should include lots of fruits and vegetables because they are good sources of antioxidants. Antioxidants protect against cardiovascular disease, cancer, and cataracts, and they are thought to slow the effects of aging. Chocolate is made up of hundreds of organic compounds, including high levels of antioxidants called catechins. (Catechins are also phenols.)

On a weight basis, the concentration of antioxidants in chocolate is higher than in red wine or green tea and 20 times higher than in tomatoes. Another piece of good news for chocolate lovers is that stearic acid, the main fatty acid in chocolate, does not appear to raise blood cholesterol levels the way other saturated fatty acids do. Dark chocolate contains more than twice the level of antioxidants found in milk chocolate. Unfortunately, white chocolate contains no antioxidants.

Polar stratospheric clouds increase the rate of ozone destruction. These clouds form over Antarctica during the cold winter months. Ozone depletion in the Arctic is less severe because the temperature generally does not get low enough for stratospheric clouds to form there.

The growth of the Antarctic ozone hole, located mostly over the continent of Antarctica, since 1985. The images were made from data supplied by total ozone-mapping spectrometers (TOMSs). The color scale depicts the total ozone values in Dobson units, with the lowest ozone densities represented by dark blue/purple.

PROBLEM 11

How many atoms share the unpaired electron in semiquinone?

14.8 RADICALS AND STRATOSPHERIC OZONE

Ozone (O_3), a major constituent of smog, is a health hazard at ground level—it inflames the airways, worsens lung ailments, and increases the risk of death from heart or lung disease. In the stratosphere, however, a layer of ozone shields the Earth from harmful solar radiation, with the greatest concentrations lying between 12 and 15 miles above the Earth's surface.

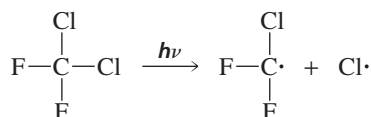
In the stratosphere, ozone acts as a filter for biologically harmful ultraviolet (UV) light that otherwise would reach the surface of the Earth. Among other effects, short-wavelength UV light can damage DNA in skin cells, causing mutations that trigger skin cancer. We owe our very existence to this protective ozone layer. According to current theories of evolution, life could not have developed on land without it. Instead most, if not all, living things would have had to remain in the ocean, where water screens out the harmful UV light.

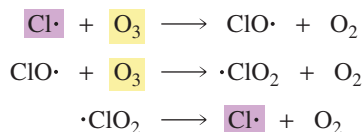
The ozone layer is thinnest at the equator and densest toward the poles. Since about 1985, scientists have noted a precipitous drop in stratospheric ozone over Antarctica. This area of ozone depletion, dubbed the "ozone hole," is unprecedented in the history of ozone observations. Scientists subsequently noted a similar decrease in ozone over Arctic regions; then, in 1988, they detected a depletion of ozone over the United States for the first time. Three years later, scientists determined that the rate of ozone depletion was two to three times faster than originally anticipated.

Strong circumstantial evidence implicated synthetic chlorofluorocarbons (CFCs)—alkanes in which all the hydrogens have been replaced by fluorine and chlorine—as a major cause of ozone depletion. These gases, known commercially as Freon, had been used extensively as cooling fluids in refrigerators and air conditioners. They were also once widely used as propellants in aerosol spray cans (deodorant, hair spray, and so on) because of their odorless, nontoxic, and nonflammable properties and because, being chemically inert, they do not react with the contents of the can. Now such use is banned, and propane and butane are used as propellants instead.

The global agreement to phase out CFCs and other ozone-depleting agents seems to be working. The ozone hole is stabilizing and it is hoped that the ozone layer will regain its density by 2070.

Chlorofluorocarbons are stable until they reach the stratosphere. There they encounter wavelengths of UV light that cause the C—Cl bond to break homolytically, generating chlorine radicals.

$$CFCl_2\text{—}Cl \xrightarrow{h\nu} F\text{—}\dot{C}(Cl)\text{—}F + Cl\cdot$$

These chlorine radicals are the ozone-removing agents. They react with ozone to form chlorine monoxide radicals and molecular oxygen. The chlorine monoxide radical then reacts with more ozone to form chlorine dioxide, which dissociates to regenerate a chlorine radical. These three steps—two of which each destroy an ozone molecule—are the propagating steps that are repeated over and over. It has been calculated that a single chlorine atom destroys 100,000 ozone molecules!

$$Cl\cdot + O_3 \longrightarrow ClO\cdot + O_2$$
$$ClO\cdot + O_3 \longrightarrow \cdot ClO_2 + O_2$$
$$\cdot ClO_2 \longrightarrow Cl\cdot + O_2$$

Artificial Blood

Clinical trials are underway to test the use of perfluorocarbons—alkanes in which all the hydrogens have been replaced by fluorines—as compounds to replace blood volume and mimic hemoglobin's ability to carry oxygen to cells and transport carbon dioxide to the lungs.

These compounds are not a true blood substitute, because blood performs many functions that artificial blood cannot. For example, white blood cells fight against infection and platelets are involved in blood clotting. However, artificial blood has several advantages in trauma situations until an actual transfusion can be done: it is safe from disease, it can be administered to any blood type, its availability does not depend on blood donors, and it can be stored longer than whole blood, which is good for only about 40 days.

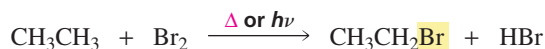
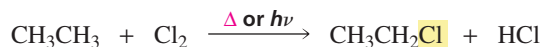
SOME IMPORTANT THINGS TO REMEMBER

- **Alkanes** are **saturated hydrocarbons.** Because they do not contain any carbon–carbon double or triple bonds, they are saturated with hydrogen.
- Alkanes are unreactive compounds because they have only strong σ bonds and atoms with no partial charges.
- In **heterolytic bond cleavage,** a bond breaks so that one of the atoms retains both of the bonding electrons; in **homolytic bond cleavage,** a bond breaks so that each of the atoms retains one of the bonding electrons.
- Alkanes undergo **radical substitution reactions** with chlorine (Cl_2) or bromine (Br_2) at high temperatures or in the presence of light to form alkyl chlorides or alkyl bromides. This substitution reaction is a **radical chain reaction** with **initiation, propagation,** and **termination steps.**
- The rate-determining step of a radical substitution reaction is removal of a hydrogen atom to form an alkyl radical.
- The relative rates of radical formation are $3° > 2° > 1° >$ methyl.
- A bromine radical is *less reactive* than a chlorine radical, so a bromine radical is *more selective* about which hydrogen atom it removes.
- Ethers form explosive peroxides when they are exposed to air.
- **A peroxide** is a **radical initiator** because it creates radicals.
- A **radical inhibitor** (an **antioxidant**) destroys radicals by creating compounds that have only paired electrons.
- If a reactant that does not have an asymmetric center undergoes a radical substitution reaction that forms a product with an asymmetric center, then a racemic mixture will be formed.
- Some biological reactions involve radicals formed by the interaction of organic molecules with metal ions. The reactions take place at the active sites of enzymes.
- The interaction of CFCs with UV light generates chlorine radicals, which are ozone-removing agents.

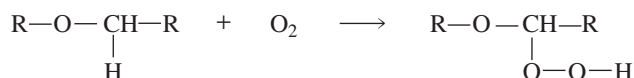
SUMMARY OF REACTIONS

1. *Alkanes* undergo radical substitution reactions with Cl_2 or Br_2 in the presence of heat or light (Sections 14.1–14.5). The mechanism of the reaction is shown on page 515.

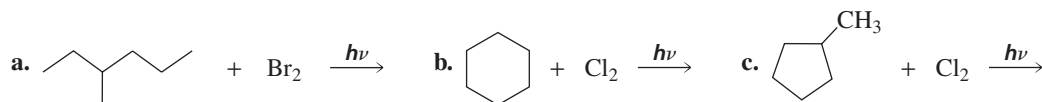
$$CH_3CH_3 + Cl_2 \xrightarrow{\Delta \text{ or } h\nu} CH_3CH_2Cl + HCl$$

$$CH_3CH_3 + Br_2 \xrightarrow{\Delta \text{ or } h\nu} CH_3CH_2Br + HBr$$

bromination is more selective than chlorination

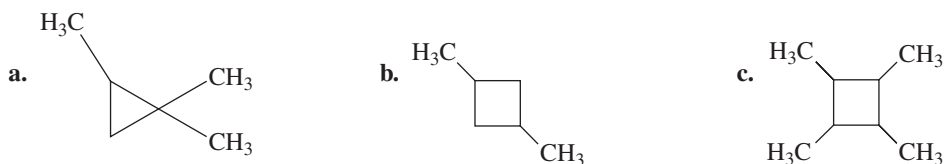
2. A radical initiator removes a hydrogen atom from an α-carbon of an ether to form a peroxide (Section 14.6). The mechanism of the reaction is shown on page 520.

$$R{-}O{-}\underset{\displaystyle H}{\underset{|}{CH}}{-}R + O_2 \longrightarrow R{-}O{-}\underset{\displaystyle O{-}O{-}H}{\underset{|}{CH}}{-}R$$

PROBLEMS

12. Draw the product(s) of each of the following reactions, disregarding stereoisomers:

a. + Br_2 $\xrightarrow{h\nu}$ **b.** + Cl_2 $\xrightarrow{h\nu}$ **c.** CH_3 + Cl_2 $\xrightarrow{h\nu}$

13. a. What alkane, with molecular formula C_5H_{12}, forms only one monochlorinated product when it is heated with Cl_2?
b. What alkane, with molecular formula C_7H_{16}, forms seven monochlorinated products (disregarding stereoisomers) when it is heated with Cl_2?

14. What is the major monochlorination product that would be obtained from treating each of the following compounds with Cl_2 in the presence of light at room temperature? Disregard stereoisomers.

a. H_3C CH_3 CH_3 **b.** H_3C CH_3 **c.** H_3C CH_3 H_3C CH_3

15. a. Would chlorination or bromination produce a greater yield of 2-halo-2,3-dimethylbutane?
b. Would chlorination or bromination be a better way to make 1-halo-2,2-dimethylpropane?

16. Show how the following compounds could be prepared from 2-methylpropane:
a. 2-bromo-2-methylpropane **b.** 2-methyl-1-propene **c.** 2-iodo-2-methylpropane

17. a. How many monochlorination products could be obtained from the radical chlorination of methylcyclohexane? Disregard stereoisomers.
b. How many monochlorination products would be obtained if all stereoisomers are included?

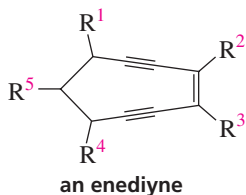
18. a. What hydrocarbon with molecular formula C_4H_{10} forms only two monochlorinated products? Both products are achiral.
b. What hydrocarbon with the same molecular formula as that in part **a** forms three monochlorinated products? One is achiral and two are chiral.

19. Using resonance contributors, explain why a catechin is an antioxidant.

20. A chemist wanted to determine experimentally the relative ease of removing a hydrogen atom from a tertiary, a secondary, and a primary carbon by a chlorine radical. He allowed 2-methylbutane to undergo chlorination at 300 °C and obtained as products 36% 1-chloro-2-methylbutane, 18% 2-chloro-2-methylbutane, 28% 2-chloro-3-methylbutane, and 18% 1-chloro-3-methylbutane. What values did he obtain for the relative ease of removing a hydrogen atom from tertiary, secondary, and primary hydrogen carbons by a chlorine radical under the conditions of his experiment?

21. Explain why the rate of bromination of methane decreases if HBr is added to the reaction mixture.

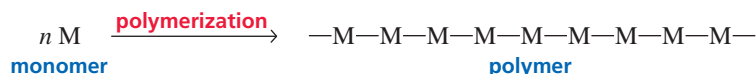
22. Enediynes are natural products with potent antitumor properties because they are able to cleave DNA. Their cytotoxic properties are due to the enediyne undergoing a cyclization reaction to form a highly reactive diradical intermediate. The intermediate abstracts hydrogen atoms from the backbone of DNA, which triggers its damage. Draw the structure of the diradical intermediate.

an enediyne

15 Synthetic Polymers

boots made of synthetic rubber

Probably no group of synthetic compounds is more important to modern life than synthetic polymers. Unlike small organic molecules, which are of interest because of their chemical properties, these giant molecules—with molecular weights ranging from thousands to millions—are interesting primarily because of their physical properties that make them useful in everyday life. Some synthetic polymers resemble natural substances, but most are quite different from materials found in nature. Such diverse products as plastic bottles, compact discs, rugs, food wrap, artificial joints, Super Glue, toys, weather stripping, automobile body parts, and shoe soles are made of synthetic polymers.

A **polymer** is a large molecule made by linking together repeating units of small molecules called **monomers.** The process of linking them together is called **polymerization.**

$$\underset{\text{monomer}}{n\,\mathrm{M}} \xrightarrow{\text{polymerization}} \underset{\text{polymer}}{\text{—M—M—M—M—M—M—M—M—M—}}$$

Polymers can be divided into two broad groups: **synthetic polymers** and **biopolymers.** Synthetic polymers are synthesized by scientists, whereas biopolymers are synthesized by cells. Examples of biopolymers are DNA—the storage molecule for genetic information; RNA and proteins—the molecules that facilitate biochemical transformations; and polysaccharides—compounds that store energy and also function as structural materials. The structures and properties of these biopolymers are presented in other chapters. In this chapter, we will explore synthetic polymers.

Humans first relied on *biopolymers* for clothing, wrapping themselves in animal skins and furs. Later, they learned to spin natural fibers into thread and to weave the thread into cloth. Today, much of our clothing is made of *synthetic polymers* (such as nylon, polyester, and polyacrylonitrile). It has been estimated that if synthetic polymers were not available, all the arable land in the United States would have to be used for the production of cotton and wool for clothing.

A **plastic** is a polymer capable of being molded. The first commercial plastic, celluloid, was invented in 1856. It was used in the manufacture of billiard balls and piano keys, replacing scarce ivory and providing a reprieve for many elephants. Celluloid was also used for motion picture film until it was replaced by cellulose acetate, a more stable polymer.

The first synthetic fiber was rayon. In 1865, the French silk industry was threatened by an epidemic that killed many silkworms. Louis Pasteur determined the source of the disease, but it was his assistant, Louis Chardonnet, who accidentally discovered the starting material for a synthetic substitute for silk when, while wiping up some spilled nitrocellulose from a table, he noticed long silk-like strands adhering to both the cloth and the table.

The first synthetic rubber was synthesized by German chemists in 1917, in response to a severe shortage of raw materials as a result of blockading during World War I.

Polymer chemistry is part of the larger discipline of **materials science,** which involves the creation of new materials with improved properties to add to the metals, glass, fabrics, and woods we currently have. Polymer chemistry has evolved into a trillion-dollar industry. Approximately 30,000 polymer patents are currently in force. We can expect scientists to develop many more new materials in the years to come.

15.1 THERE ARE TWO MAJOR CLASSES OF SYNTHETIC POLYMERS

Synthetic polymers can be divided into two major classes: chain-growth polymers and step-growth polymers. **Chain-growth polymers** are made by **chain reactions**—the addition of monomers to the end of a growing chain. The end of a growing chain is reactive because it is a radical, a cation, or an anion. Polystyrene—used for hot drink cups, egg cartons, and insulation, among other things—is an example of a chain-growth polymer. Polystyrene is pumped full of air to produce the material used for insulation in house construction.

Chain-growth polymers are also called addition polymers.

Chain-growth polymers are made by chain reactions.

$$CH_2{=}CH(C_6H_5) \quad CH_2{=}CH(C_6H_5) \quad CH_2{=}CH(C_6H_5) \longrightarrow -CH_2-CH(C_6H_5)-[CH_2-CH(C_6H_5)]_n-CH_2-CH(C_6H_5)-$$

styrene

repeat unit

polystyrene
a chain-growth polymer

Step-growth polymers are made by linking monomers as a result of removing (in most cases) a small molecule, generally water or an alcohol. The monomers have reactive functional groups at each end. Unlike chain-growth polymerization, which requires the individual monomers to add to the end of a growing chain, step-growth polymerization allows any two reactive monomers, dimers, trimers, etc. to be linked. Dacron is an example of a step-growth polymer.

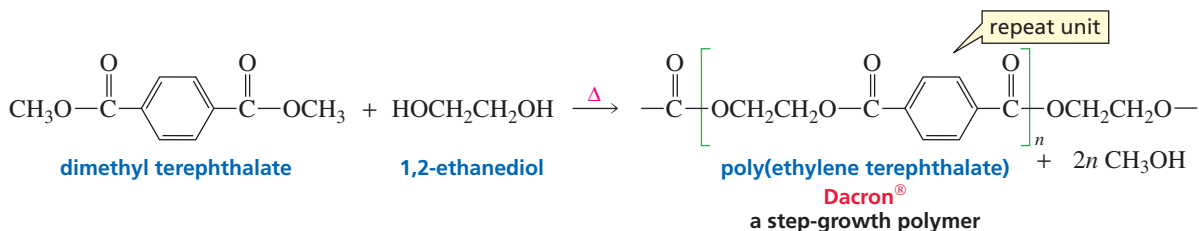
Step-growth polymers are also called condensation polymers.

Step-growth polymers are made by linking molecules with reactive functional groups at each end.

$$CH_3O-\overset{O}{\overset{\|}{C}}-C_6H_4-\overset{O}{\overset{\|}{C}}-OCH_3 + HOCH_2CH_2OH \xrightarrow{\Delta} -\overset{O}{\overset{\|}{C}}-\left[OCH_2CH_2O-\overset{O}{\overset{\|}{C}}-C_6H_4-\overset{O}{\overset{\|}{C}}\right]_n-OCH_2CH_2O- + 2n\,CH_3OH$$

dimethyl terephthalate　　1,2-ethanediol

repeat unit

poly(ethylene terephthalate)
Dacron®
a step-growth polymer

15.2 CHAIN-GROWTH POLYMERS

The monomers used most commonly in chain-growth polymerization are ethylene (ethene) and substituted ethylenes ($CH_2=CHR$). Polymers formed from these monomers are called **vinyl polymers.** Some of the many vinyl polymers are listed in Table 15.1.

Table 15.1 Some Important Chain-Growth Polymers and Their Uses

Monomer	Repeating unit	Polymer name	Uses
$CH_2=CH_2$	$-CH_2-CH_2-$	polyethylene	toys, water bottles, grocery bags
$CH_2=CH(Cl)$	$-CH_2-CH(Cl)-$	poly(vinyl chloride)	shampoo bottles, pipe, siding, flooring, clear food packaging
$CH_2=CH(CH_3)$	$-CH_2-CH(CH_3)-$	polypropylene	molded caps, margarine tubs, indoor/outdoor carpeting, plastic chairs
$CH_2=CH(C_6H_5)$	$-CH_2-CH(C_6H_5)-$	polystyrene	compact disc jackets, egg cartons, hot drink cups, insulation
$CF_2=CF_2$	$-CF_2-CF_2-$	poly(tetrafluoroethylene) Teflon	nonstick surfaces, liners, cable insulation
$CH_2=CH(C\equiv N)$	$-CH_2-CH(C\equiv N)-$	poly(acrylonitrile) Orlon, Acrilan	rugs, blankets, yarn, apparel, simulated fur
$CH_2=C(CH_3)-COCH_3$ (C=O)	$-CH_2-C(CH_3)(COCH_3)-$ (C=O)	poly(methyl methacrylate) Plexiglas, Lucite	shatter-resistant alternative to glass
$CH_2=CH-OCCH_3$ (C=O)	$-CH_2-CH(OCCH_3)-$ (C=O)	poly(vinyl acetate)	white glue, adhesives

Chain-growth polymerization proceeds by one of three mechanisms: **radical polymerization, cationic polymerization,** or **anionic polymerization.** Each mechanism has three distinct phases: an *initiation step* that starts the polymerization, *propagation steps* that allow the chain to grow, and *termination steps* that stop the growth of the polymer chain. We will see that the mechanism for a given chain-growth polymerization reaction depends on the structure of the monomer and on the initiator used to activate the monomer.

Radical Polymerization

The chain-initiating, chain-propagating, and chain-terminating steps that occur in *radical polymerization* are similar to the steps that take place in the radical reactions discussed in Section 14.2.

Radical polymerization requires a radical initiator. The radical initiator can be any compound with a weak bond that readily undergoes homolytic cleavage by heat or light to form radicals sufficiently energetic to convert an alkene into a radical.

MECHANISM FOR RADICAL POLYMERIZATION

initiation steps

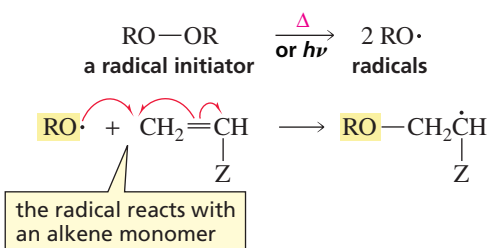
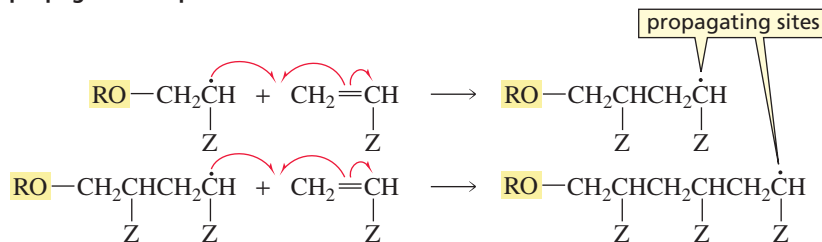
$$\underset{\text{a radical initiator}}{RO{-}OR} \xrightarrow[\text{or } h\nu]{\Delta} \underset{\text{radicals}}{2\ RO\cdot}$$

$$RO\cdot + CH_2{=}CH(Z) \longrightarrow RO{-}CH_2\dot{C}H(Z)$$

the radical reacts with an alkene monomer

propagation steps

$$RO{-}CH_2\dot{C}H(Z) + CH_2{=}CH(Z) \longrightarrow RO{-}CH_2CH(Z)CH_2\dot{C}H(Z)$$

$$RO{-}CH_2CH(Z)CH_2\dot{C}H(Z) + CH_2{=}CH(Z) \longrightarrow RO{-}CH_2CH(Z)CH_2CH(Z)CH_2\dot{C}H(Z)$$

propagating sites

- The initiator breaks homolytically into radicals, and each of these radicals can react with a monomer, creating a monomer radical.
- In the first propagation step, the monomer radical reacts with another monomer, converting it into a radical.
- This radical reacts with another monomer, adding a new subunit to the chain. Notice that the unpaired electron is at the end of the unit most recently added to the chain. This is called the **propagating site.**

Hundreds or even thousands of alkene monomers can add, one at a time, to the growing chain. Eventually, the chain reaction stops because the propagating sites are destroyed in a termination step. Propagating sites are destroyed when

- two chains combine at their propagating sites (chain combination).
- a chain undergoes chain transfer.

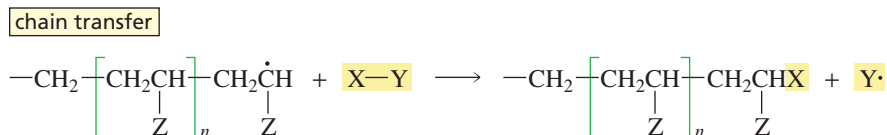
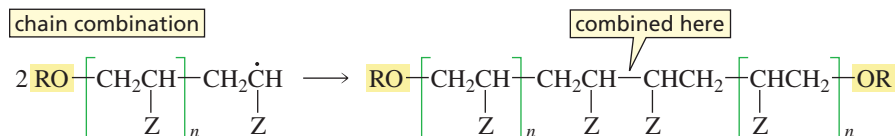
termination steps

chain combination

$$2\ RO{-}[CH_2CH(Z)]_n{-}CH_2\dot{C}H(Z) \longrightarrow RO{-}[CH_2CH(Z)]_n{-}CH_2CH(Z){-}CH(Z)CH_2{-}[CH(Z)CH_2]_n{-}OR$$

combined here

chain transfer

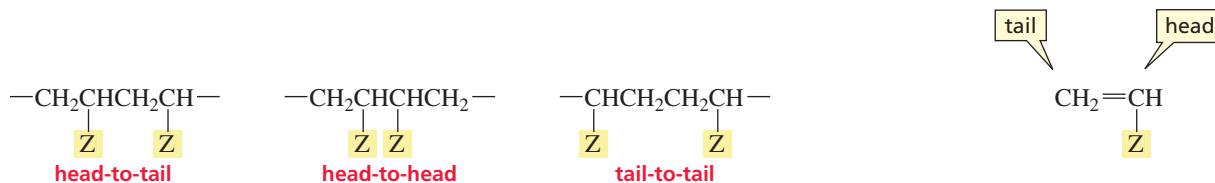
$$-CH_2{-}[CH_2CH(Z)]_n{-}CH_2\dot{C}H(Z) + X{-}Y \longrightarrow -CH_2{-}[CH_2CH(Z)]_n{-}CH_2CH(Z)X + Y\cdot$$

In **chain transfer,** the growing chain reacts with a molecule XY in a manner that allows X· to terminate the chain, leaving behind Y· to initiate a new chain. Molecule XY can be a solvent, a radical initiator, or any molecule with a bond that can readily be cleaved homolytically. Chain transfer can be used to control the molecular weight of the polymer.

As long as the polymer has a high molecular weight, the groups (RO and X) at the ends of the polymer chains—arising from initiation and chain transfer—are relatively unimportant in determining its physical properties and are generally not even specified; it is the rest of the molecule that determines the properties of the polymer.

Chain-growth polymerization exhibits a marked preference for **head-to-tail addition,** in which the head of one monomer is attached to the tail of another. (Notice that head-to-tail addition of a substituted ethylene results in a polymer in which every other carbon bears a substituent.)

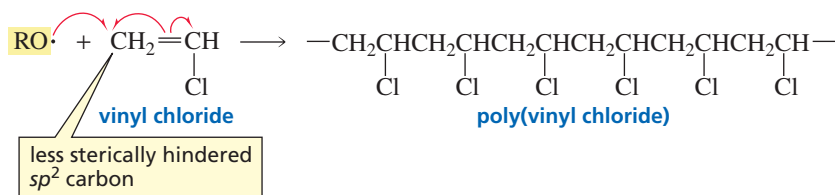
—CH2CHCH2CH— (Z, Z) **head-to-tail**

—CH2CHCHCH2— (Z, Z) **head-to-head**

—CHCH2CH2CH— (Z, Z) **tail-to-tail**

Two factors cause head-to-tail addition to be favored. First, there is less steric hindrance at the unsubstituted sp^2 carbon of the alkene; therefore, the propagating site attacks it preferentially.

RO· + CH2=CH(Cl) ⟶ —CH2CHCH2CHCH2CHCH2CHCH2CHCH2CH— (Cl on each CH)

vinyl chloride — poly(vinyl chloride)

less sterically hindered sp^2 carbon

Second, radicals formed by addition to the unsubstituted sp^2 carbon can be stabilized by the substituent attached to the other sp^2 carbon. For example, when Z is a phenyl substituent, the benzene ring stabilizes the radical by electron delocalization.

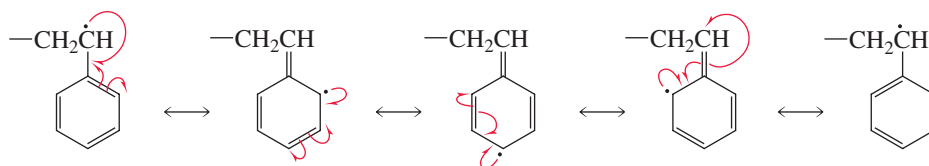
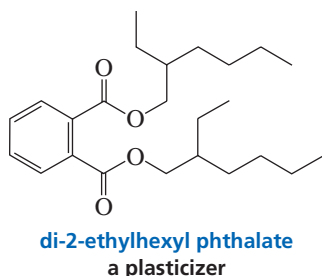
—CH2ĊH(C6H5) ⟷ —CH2CH= ⟷ —CH2CH= ⟷ —CH2CH= ⟷ —CH2ĊH(C6H5)

Monomers that most readily undergo chain-growth polymerization by a radical mechanism are those in which the substituent Z is a group able to stabilize the growing radical species by electron delocalization and/or is an electron-withdrawing group.

Table 15.2 Examples of Alkenes That Undergo Radical Polymerization

CH2=CH–C6H5 **styrene**	CH2=CH–C≡N **acrylonitrile**	CH2=CH–CH=CH2 **1,3-butadiene**
CH2=CH–Cl **vinyl chloride**	CH2=CH–OC(=O)CH3 **vinyl acetate**	CH2=C(CH3)–C(=O)OCH3 **methyl methacrylate**

Radical polymerization of methyl methacrylate forms a clear plastic known as Plexiglas. The largest window in the world, made of a single piece of Plexiglas (54 ft long, 18 ft high, and 13 in. thick), houses the sharks and barracudas in the Monterey Bay Aquarium.

Plexiglas windows

di-2-ethylhexyl phthalate
a plasticizer

A plasticizer can be dissolved into a polymer to make it more flexible. The **plasticizer** decreases the attractions between the polymer chains, thereby allowing them to slide past one another. The most widely used plasticizer, di-2-ethylhexyl phthalate, is added to poly(vinyl chloride)—normally a brittle polymer—to make products such as vinyl raincoats, shower curtains, and garden hoses.

An important property to consider in choosing a plasticizer is its permanence—that is, how well the plasticizer remains in the polymer. The "new-car smell" appreciated by car owners is the odor of the plasticizer that has vaporized from the vinyl upholstery. When a significant amount of the plasticizer has evaporated, the upholstery becomes brittle and cracks.

Teflon: An Accidental Discovery

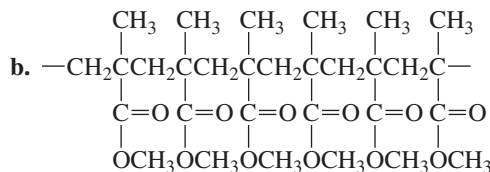
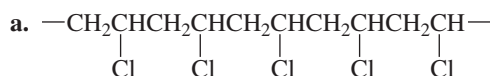
Teflon is a polymer of tetrafluoroethylene (Table 15.1). In 1938, a scientist needed some tetrafluoroethylene for the synthesis of what he hoped would be a new refrigerant. When he opened the cylinder of tetrafluoroethylene, no gas came out. He weighed the cylinder and found that it weighed more than an identical empty cylinder. In fact, it weighed the same as what a cylinder full of tetrafluoroethylene would weigh. Wondering what the cylinder contained, he cut it open and found a slippery polymer. Investigating the polymer further, he found that it was chemically inert to almost everything and could not be melted. In 1961, the first frying pan with a nonstick Teflon coating—"The Happy Pan"— was introduced to the public. Teflon is also used as a lubricant to reduce friction and in pipework that carries corrosive chemicals.

PROBLEM 1♦

What monomer would you use to form each of the following polymers?

a. $—CH_2CHCH_2CHCH_2CHCH_2CHCH_2CH—$ (each CH bearing Cl)

b. $—CH_2CCH_2CCH_2CCH_2CCH_2CCH_2C—$ (each C bearing CH_3 and $C{=}O$ with OCH_3)

c. $—CF_2CF_2CF_2CF_2CF_2CF_2CF_2CF_2CF_2CF_2—$

PROBLEM 2

Draw a segment of polystyrene that contains two head-to-head, two tail-to-tail, and two head-to-tail linkages.

PROBLEM 3

Show the mechanism for the formation of a segment of poly(vinyl chloride) that contains three units of vinyl chloride and is initiated by hydrogen peroxide.

Branching of the Polymer Chain

If the propagating site removes a hydrogen atom from a chain, a branch can grow off the chain at that point. The propagating site can remove a hydrogen atom from a different polymer chain or from the same polymer chain.

propagation site

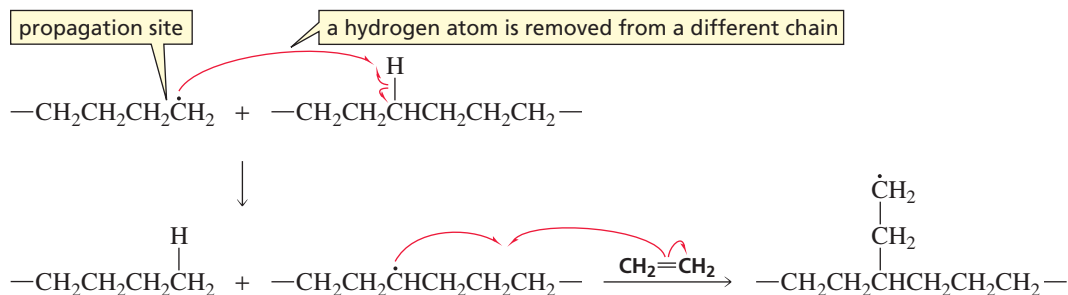
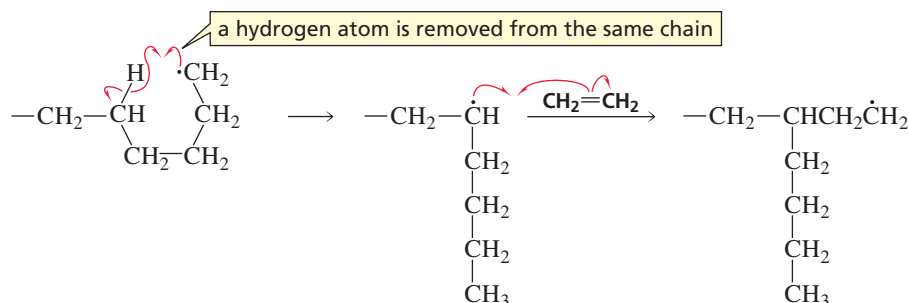
a hydrogen atom is removed from a different chain

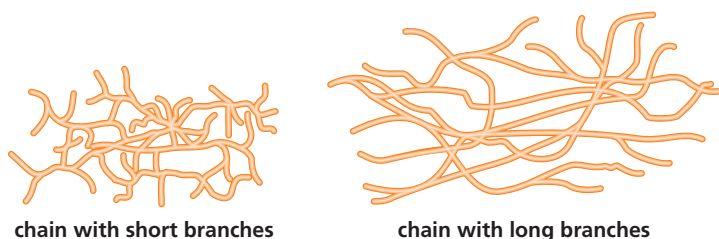
$—CH_2CH_2CH_2\dot{C}H_2 + —CH_2CH_2CH(H)CH_2CH_2CH_2—$

$\downarrow$

$—CH_2CH_2CH_2CH_2(H) + —CH_2CH_2\dot{C}HCH_2CH_2CH_2— \xrightarrow{CH_2=CH_2} —CH_2CH_2CH(CH_2\dot{C}H_2)CH_2CH_2CH_2—$

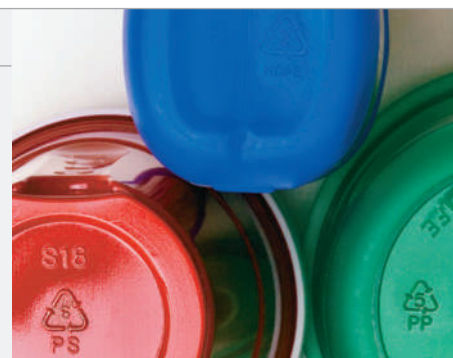
a hydrogen atom is removed from the same chain

$$-CH_2-CH(H)\cdots\dot{C}H_2\,(\text{ring: }CH-CH_2-CH_2-CH_2-\dot{C}H_2) \longrightarrow -CH_2-\dot{C}H(CH_2CH_2CH_2CH_3) \xrightarrow{CH_2=CH_2} -CH_2-CH(CH_2CH_2CH_2CH_3)CH_2\dot{C}H_2$$

Removing a hydrogen atom from a carbon near the end of a chain leads to short branches, whereas removing a hydrogen atom from a carbon near the middle of a chain results in long branches. Short branches are more likely to be formed than long ones because the ends of the chain are more accessible.

chain with short branches chain with long branches

Branched polymers are more flexible.

Branching greatly affects the physical properties of the polymer. Unbranched chains can pack together more closely than branched chains can. Consequently, linear polyethylene (known as high-density polyethylene) is a relatively hard plastic, used for the production of such things as artificial hip joints; whereas branched polyethylene (low-density polyethylene) is a much more flexible polymer, used for trash bags and dry-cleaning bags.

Recycling Symbols

When plastics are recycled, the various types must be separated from one another. To aid in the separation, many states require manufacturers to place a recycling symbol on their products to indicate the type of plastic it is. You are probably familiar with these symbols, which are often embossed on the bottom of plastic containers. The symbols consist of three arrows around one of seven numbers; an abbreviation below the symbol indicates the type of polymer from which the container is made. The lower the number in the middle of the symbol, the greater is the ease with which the material can be recycled: 1 (PET) stands for poly(ethylene terephthalate), 2 (HDPE) for high-density polyethylene, 3 (V) for poly(vinyl chloride), 4 (LDPE) for low-density polyethylene, 5 (PP) for polypropylene, 6 (PS) for polystyrene, and 7 for all other plastics.

recycling symbols

PROBLEM 4

Polyethylene can be used for the production of beach chairs as well as beach balls. Which of these items is made from more highly branched polyethylene?

Cationic Polymerization

In cationic polymerization, the initiator is an electrophile (generally a proton) that adds to the monomer, causing it to become a carbocation. The initiator cannot be an acid such as HCl because its conjugate base (Cl^-) will be able to react with the carbocation. Thus, the initiator often used in cationic polymerization is a compound with an incomplete octet, such as BF_3, and water. Notice that the reaction follows the rule that governs electrophilic addition reactions—that is, the electrophile (the proton initiator) adds to the *sp*^{2} carbon bonded to the most hydrogens (Section 6.3).

MECHANISM FOR CATIONIC POLYMERIZATION

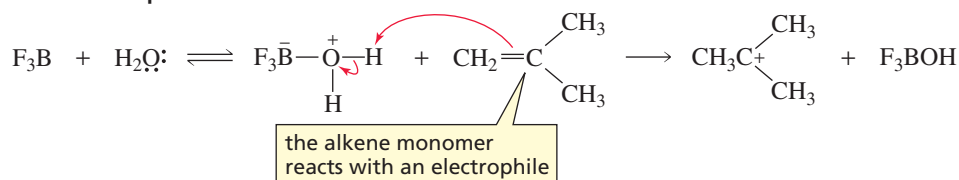
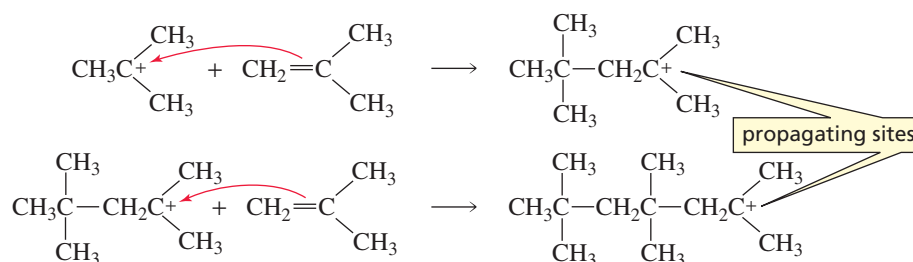
initiation steps

$$F_3B + H_2\ddot{O}: \rightleftharpoons F_3\bar{B}-\overset{+}{O}H-H + CH_2{=}C(CH_3)_2 \longrightarrow CH_3\overset{+}{C}(CH_3)_2 + F_3BOH$$

the alkene monomer reacts with an electrophile

propagating steps

$$CH_3\overset{+}{C}(CH_3)_2 + CH_2{=}C(CH_3)_2 \longrightarrow CH_3C(CH_3)_2-CH_2\overset{+}{C}(CH_3)_2$$

$$CH_3C(CH_3)_2-CH_2\overset{+}{C}(CH_3)_2 + CH_2{=}C(CH_3)_2 \longrightarrow CH_3C(CH_3)_2-CH_2C(CH_3)_2-CH_2\overset{+}{C}(CH_3)_2$$

propagating sites

- The cation formed in the initiation step reacts with a second monomer, forming a new cation that reacts in turn with a third monomer. As each subsequent monomer adds to the chain, the new positively charged propagating site is at the end of the most recently added unit.

Cationic polymerization can be terminated by

- loss of a proton;
- addition of a nucleophile to the propagating site;
- a chain-transfer reaction with the solvent (XY).

termination steps

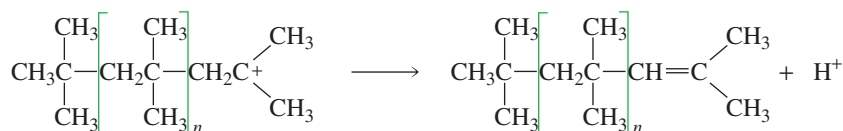
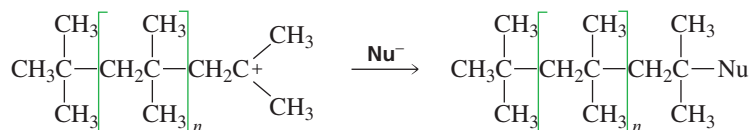
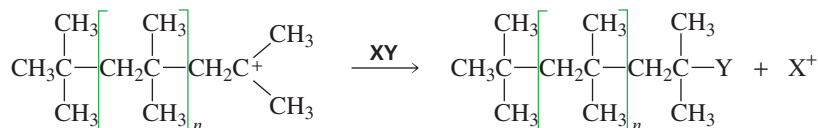
loss of a proton

$$CH_3C(CH_3)_2-[CH_2C(CH_3)_2]_n-CH_2\overset{+}{C}(CH_3)_2 \longrightarrow CH_3C(CH_3)_2-[CH_2C(CH_3)_2]_n-CH{=}C(CH_3)_2 + H^+$$

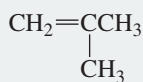
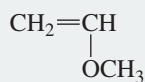
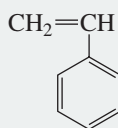
reaction with a nucleophile

$$CH_3C(CH_3)_2-[CH_2C(CH_3)_2]_n-CH_2\overset{+}{C}(CH_3)_2 \xrightarrow{Nu^-} CH_3C(CH_3)_2-[CH_2C(CH_3)_2]_n-CH_2C(CH_3)_2-Nu$$

chain-transfer reaction with the solvent

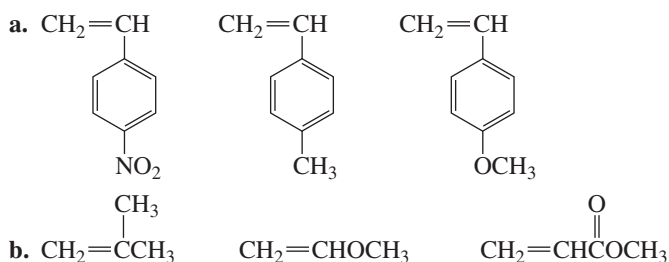
$$CH_3C(CH_3)_2-[CH_2C(CH_3)_2]_n-CH_2\overset{+}{C}(CH_3)_2 \xrightarrow{XY} CH_3C(CH_3)_2-[CH_2C(CH_3)_2]_n-CH_2C(CH_3)_2-Y + X^+$$

Monomers that are best able to undergo polymerization by a cationic mechanism are those with substituents that can stabilize the positive charge at the propagating site either

by hyperconjugation (the first compound in Table 15.3; Section 6.2) or by donating electrons by resonance (the other two compounds in the table; Section 7.9).

Table 15.3 Examples of Alkenes That Undergo Cationic Polymerization

$CH_2{=}C(CH_3)CH_3$	$CH_2{=}CHOCH_3$	$CH_2{=}CHC_6H_5$
isobutylene	methyl vinyl ether	styrene

PROBLEM 5♦

List the following groups of monomers in order from most able to least able to undergo cationic polymerization:

a. $CH_2{=}CH{-}C_6H_4{-}NO_2$ $CH_2{=}CH{-}C_6H_4{-}CH_3$ $CH_2{=}CH{-}C_6H_4{-}OCH_3$

b. $CH_2{=}C(CH_3)CH_3$ $CH_2{=}CHOCH_3$ $CH_2{=}CHC({=}O)OCH_3$

Anionic Polymerization

In anionic polymerization, the initiator is a nucleophile that reacts with the monomer to form a propagating site that is an anion. Nucleophilic attack on an alkene does not occur readily because alkenes are themselves electron rich. Therefore, the initiator must be a very good nucleophile, such as sodium amide or butyllithium (Bu^- Li^+), and the alkene must contain a substituent that can withdraw electrons by resonance, which will decrease the electron density of the double bond.

MECHANISM FOR ANIONIC POLYMERIZATION

initiation step

$$\ddot{Bu}^-\ Li^+ + CH_2{=}CH(C_6H_5) \longrightarrow Bu{-}CH_2\ddot{C}H^-(C_6H_5)$$

the alkene monomer reacts with a nucleophile

propagation steps

$$Bu{-}CH_2\ddot{C}H^-(C_6H_5) + CH_2{=}CH(C_6H_5) \longrightarrow Bu{-}CH_2CH(C_6H_5){-}CH_2\ddot{C}H^-(C_6H_5)$$

$$Bu{-}CH_2CH(C_6H_5){-}CH_2\ddot{C}H^-(C_6H_5) + CH_2{=}CH(C_6H_5) \longrightarrow Bu{-}CH_2CH(C_6H_5){-}CH_2CH(C_6H_5){-}CH_2\ddot{C}H^-(C_6H_5)$$

propagating sites

The chain can be terminated by reaction with an impurity in the reaction mixture. If all impurities are rigorously excluded, chain propagation will continue until all the monomer has been consumed. At this point, the propagating site will still be active, so the polymerization reaction will continue if more monomer is added to the system. Such nonterminated chains are called **living polymers** because the chains remain active until they are terminated ("killed").

Living polymers are most common in anionic polymerization because the chains cannot be terminated by proton loss from the polymer (as they can in cationic polymerization) or by chain combination (as they can in radical polymerization).

Alkenes that undergo polymerization by an anionic mechanism are those that can stabilize the negatively charged propagating site by resonance electron withdrawal (Table 15.4).

Table 15.4 Examples of Alkenes That Undergo Anionic Polymerization

acrolein	methyl methacrylate	styrene
$CH_2=CH-CH=O$	$CH_2=C(CH_3)-C(=O)OCH_3$	$CH_2=CH-C_6H_5$

Super Glue is a polymer of methyl α-cyanoacrylate. Because the monomer has two electron-withdrawing groups, it requires only a moderately good nucleophile to initiate anionic polymerization, such as surface-absorbed water. You may well have experienced this reaction if you have ever spilled a drop of Super Glue on your fingers. A nucleophilic group on the surface of the skin initiates the polymerization reaction, with the result that two fingers can become firmly glued together.

$$\underset{\text{methyl }\alpha\text{-cyanoacrylate}}{CH_2=C(C\equiv N)(C(=O)OCH_3)} \longrightarrow \underset{\text{Super Glue}^{®}}{-CH_2C(C\equiv N)(C{=}O\,OCH_3)-CH_2C(C\equiv N)(C{=}O\,OCH_3)-CH_2C(C\equiv N)(C{=}O\,OCH_3)-CH_2\left[-C(C\equiv N)(C{=}O\,OCH_3)-CH_2-\right]_n C(C\equiv N)(C{=}O\,OCH_3)-CH_2C(C\equiv N)(C{=}O\,OCH_3)-}$$

The ability to form covalent bonds with groups on the surfaces of the objects to be glued together is what gives Super Glue its amazing strength. Polymers similar to Super Glue—namely, butyl, isobutyl, or octyl esters rather than methyl esters—are used by surgeons to close wounds.

PROBLEM 6♦

List the following groups of monomers in order from most able to least able to undergo anionic polymerization:

a. $CH_2=CH-C_6H_4-NO_2$ $CH_2=CH-C_6H_4-CH_3$ $CH_2=CH-C_6H_4-OCH_3$ (para-substituted)

b. $CH_2=CHCH_3$ $CH_2=CHCl$ $CH_2=CHC\equiv N$

What Determines the Mechanism?

We have seen that the substituent attached to the alkene determines the mechanism for chain-growth polymerization. Alkenes with substituents that can stabilize radicals readily undergo radical polymerization, alkenes with electron-donating substituents that can stabilize cations undergo cationic polymerization, and alkenes with electron-withdrawing substituents that can stabilize anions undergo anionic polymerizations.

Some alkenes undergo polymerization by more than one mechanism. For example, styrene can undergo polymerization by radical, cationic, and anionic mechanisms because the phenyl group can stabilize benzylic radicals, benzylic cations, and benzylic anions. The mechanism followed for its polymerization depends on the nature of the initiator chosen to start the reaction.

PROBLEM 7

Explain, using resonance structures, why Super Glue is formed by anionic polymerizarion.

PROBLEM 8♦

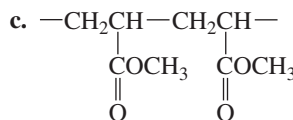
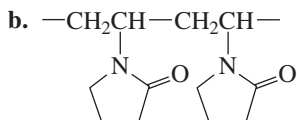
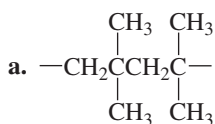
Why does methyl methacrylate not undergo cationic polymerization?

PROBLEM 9♦

Which monomer and which type of initiator would you use to synthesize each of the following polymers?

a. $-CH_2C(CH_3)_2CH_2C(CH_3)_2-$

b. $-CH_2CH-CH_2CH-$ (each CH bearing an N of a 2-pyrrolidinone ring)

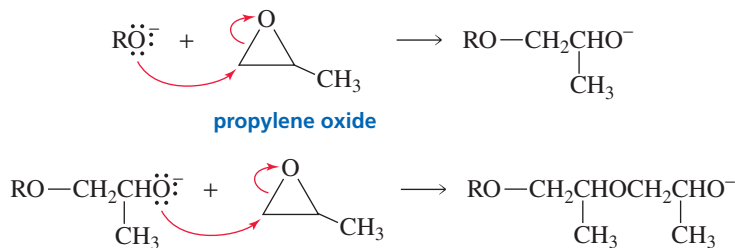
c. $-CH_2CH(COCH_3)-CH_2CH(COCH_3)-$ (each $COCH_3$ with C=O)

Ring-Opening Polymerizations

Although ethylene and substituted ethylenes are the monomers most commonly used for the synthesis of chain-growth polymers, other compounds can polymerize as well. For example, epoxides can undergo chain-growth polymerization via a ring-opening reaction. Polymerization reactions that involve ring-opening reactions are called **ring-opening polymerizations.**

If the initiator is a nucleophile, polymerization occurs by an anionic mechanism. From what you know about the reactions of epoxides, you should not be surprised that the nucleophile attacks the less sterically hindered carbon of the epoxide (Section 9.8).

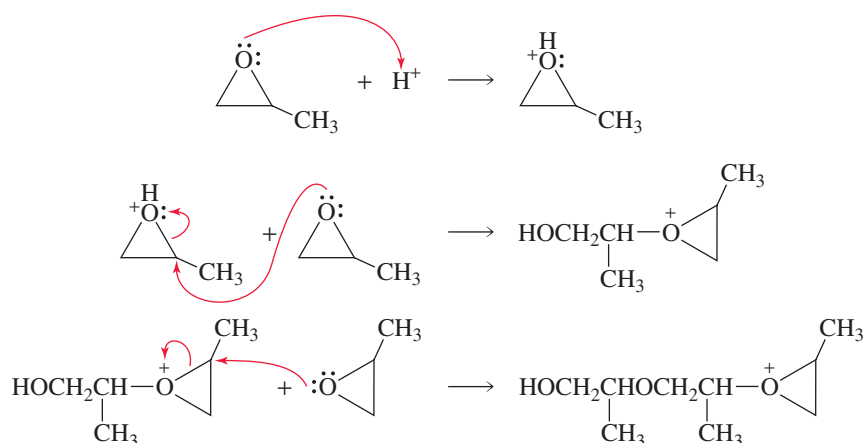
$$RO^- + \text{propylene oxide} \longrightarrow RO-CH_2CH(CH_3)O^-$$

propylene oxide

$$RO-CH_2CH(CH_3)O^- + \text{propylene oxide} \longrightarrow RO-CH_2CH(CH_3)OCH_2CH(CH_3)O^-$$

If the initiator is an acid, epoxides are polymerized by a cationic mechanism. Notice that under acidic conditions, the nucleophile attacks the more substituted carbon of the epoxide (Section 9.8).

$$\text{propylene oxide} + H^+ \longrightarrow \text{protonated propylene oxide } (^{+}\ddot{O}H,\ CH_3)$$

$$\text{protonated propylene oxide} + \text{propylene oxide} \longrightarrow HOCH_2CH(CH_3)-\overset{+}{O}\text{(epoxide ring, } CH_3)$$

$$HOCH_2CH(CH_3)-\overset{+}{O}\text{(epoxide ring, } CH_3) + :\ddot{O}\text{(epoxide ring, } CH_3) \longrightarrow HOCH_2CH(CH_3)OCH_2CH(CH_3)-\overset{+}{O}\text{(epoxide ring, } CH_3)$$

PROBLEM 10

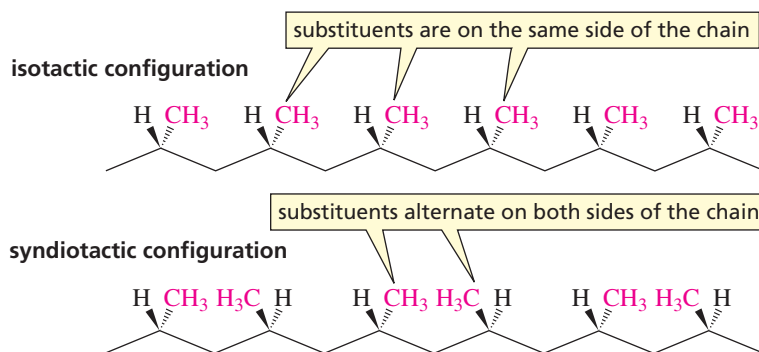
Explain why, when propylene oxide undergoes anionic polymerization, nucleophilic attack occurs at the less substituted carbon of the epoxide, but when it undergoes cationic polymerization, nucleophilic attack occurs at the more substituted carbon.

PROBLEM 11

Show the polymerization of 2,2-dimethyloxirane by

a. an anionic mechanism. **b.** a cationic mechanism.

15.3 STEREOCHEMISTRY OF POLYMERIZATION • ZIEGLER–NATTA CATALYSTS

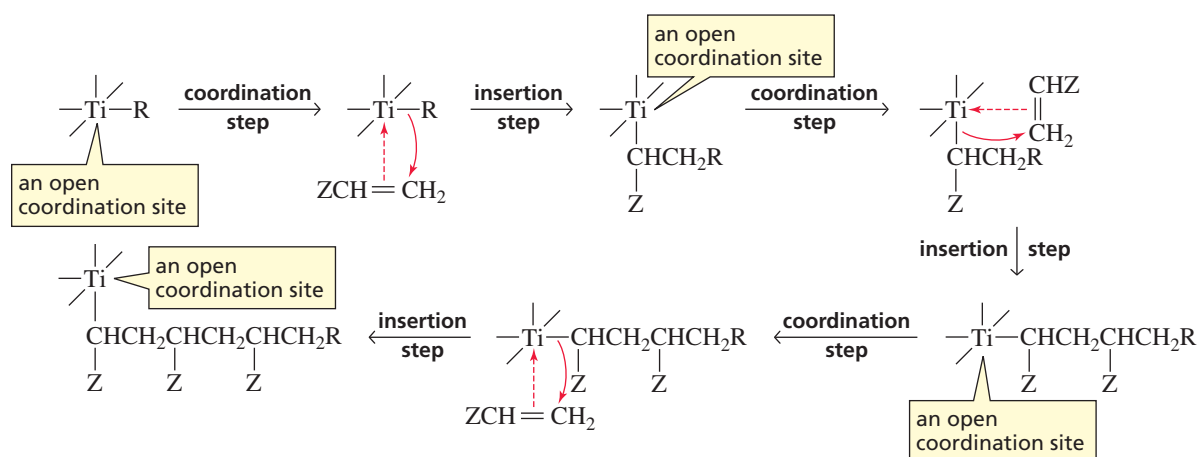
Polymers formed from monosubstituted ethylenes can exist in three configurations: isotactic, syndiotactic, and atactic. An **isotactic polymer** has all of its substituents on the same side of the fully extended carbon chain. (*Iso* and *taxis* are the Greek terms for "the same" and "order," respectively.) In a **syndiotactic polymer** (*syndio* means "alternating"), the substituents regularly alternate on both sides of the carbon chain. The substituents in an **atactic polymer** are randomly oriented.

The configuration of the polymer affects its physical properties. Polymers in the isotactic or syndiotactic configuration are more likely to be rigid solids, because positioning the substituents in a regular order allows for a more regular packing arrangement. Polymers in the atactic configuration are more disordered and cannot pack together as well, so these polymers are less rigid and, therefore, softer.

In 1953, Karl Ziegler and Giulio Natta found that the configuration of a polymer could be controlled if the growing end of the chain and the incoming monomer were coordinated with an aluminum–titanium initiator. These initiators are now called **Ziegler–Natta catalysts.** Whether the chain is isotactic or syndiotactic depends on the particular catalyst employed. These catalysts revolutionized the field of polymer

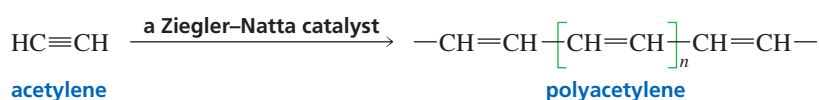
chemistry because they allow the synthesis of stronger and stiffer polymers that have greater resistance to cracking and heat.

A proposed mechanism for Ziegler–Natta-catalyzed polymerization of a substituted ethylene is shown here.

MECHANISM FOR ZIEGLER–NATTA-CATALYZED POLYMERIZATION OF A SUBSTITUTED ETHYLENE

Ti—R (an open coordination site) —coordination step→ Ti—R + ZCH═CH$_2$ —insertion step→ Ti—CHCH$_2$R (Z) (an open coordination site) —coordination step→ Ti←CHZ═CH$_2$, CHCH$_2$R (Z) —insertion step→ Ti—CHCH$_2$CHCH$_2$R (Z, Z) (an open coordination site) —coordination step→ Ti—CHCH$_2$CHCH$_2$R (Z, Z) + ZCH═CH$_2$ —insertion step→ Ti—CHCH$_2$CHCH$_2$CHCH$_2$R (Z, Z, Z) (an open coordination site)

- The monomer forms a complex with titanium (dotted arrow) at an open coordination site—that is, a site available to accept electrons.
- The coordinated alkene is inserted between the titanium and the growing polymer (R), thereby lengthening the polymer chain.
- Because a new coordination site opens up during insertion of the monomer, the process can be repeated over and over.

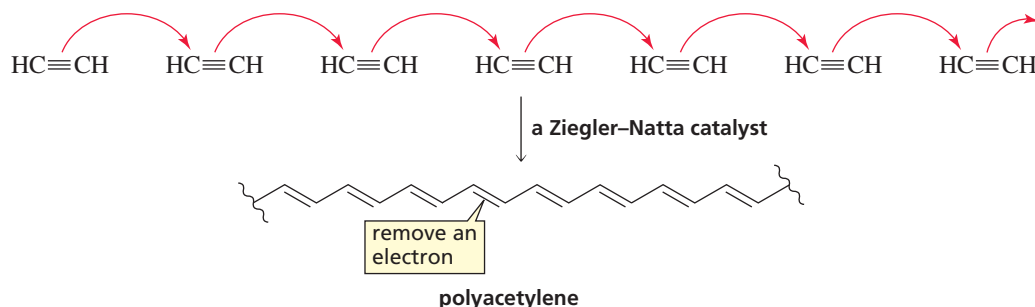
Polyacetylene is another polymer prepared by a Ziegler–Natta process. It can be converted to a **conducting polymer** because the conjugated double bonds in polyacetylene allow electron transport down its backbone after several electrons are removed from or added to the backbone (Section 15.4).

$$\underset{\text{acetylene}}{HC\equiv CH} \xrightarrow{\text{a Ziegler–Natta catalyst}} \underset{\text{polyacetylene}}{—CH{=}CH{+}CH{=}CH{+}_n CH{=}CH—}$$

15.4 ORGANIC COMPOUNDS THAT CONDUCT ELECTRICITY

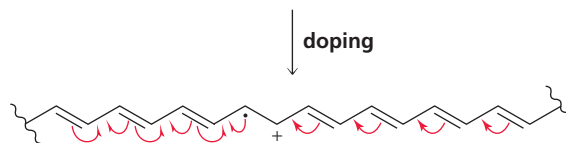
In order for an organic compound to conduct electricity, its electrons must be delocalized so that they can move through the compound just like electrons can move along a copper wire. The first organic compound able to conduct electricity was prepared by polymerizing acetylene using a Ziegler–Natta catalyst.

HC≡CH HC≡CH HC≡CH HC≡CH HC≡CH HC≡CH HC≡CH

↓ a Ziegler–Natta catalyst

remove an electron

polyacetylene

The electrons in polyacetylene are not able to move along the length of the chain easily enough to conduct electricity well. However, if electrons are removed from or added to the chain (a process called "doping"), then the electrons can move down the chain and the polymer (with some refinements) can conduct electricity as well as copper can.

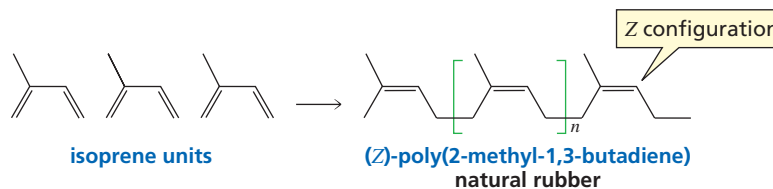
doping

Polyacetylene is very sensitive to air and moisture, which limits its technological applications. However, many other conducting polymers have been developed; they all have a chain of conjugated double bonds.

An important property of conducting polymers is that they are very light. As a result, they are used to coat airplanes to prevent lightning from damaging the interior of the aircraft. The buildup of static electricity can be prevented by coating an insulator with a thin layer of conducting polymer. Conducting polymers are also used in LED (light emitting diode) displays. LEDs emit light in response to an electric current—a process known as electroluminescence. LEDs are used for full color displays in flat-screen TVs, cell phones, and the instrument panels in cars and airplanes. Continued research should lead to many more applications for conducting polymers. One such area is the development of "smart structures," such as golf clubs that will adapt to the golfer's swing. Smart skis (that do not vibrate while skiing) have already been created.

15.5 POLYMERIZATION OF DIENES • NATURAL AND SYNTHETIC RUBBER

When the bark of a rubber tree is cut, a sticky, white liquid oozes out. This same liquid is found inside the stalks of dandelions and milkweed. In fact, more than 400 plants produce this substance. The sticky material is *latex*, a suspension of rubber particles in water. Its biological function is to protect the plant after an injury by covering the wound like a bandage.

Natural rubber is a polymer of 2-methyl-1,3-butadiene, also called isoprene. On average, a molecule of rubber contains 5000 isoprene units.

latex being collected from a rubber tree

All the double bonds in natural rubber have the *Z* configuration. Rubber is a waterproof material because its tangled hydrocarbon chains have no affinity for water. Charles Macintosh was the first to use rubber as a waterproof coating for raincoats.

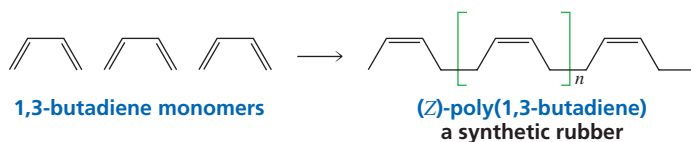
Gutta-percha (from the Malaysian words *getah*, meaning "gum," and *percha*, meaning "tree") is a naturally occurring isomer of rubber in which all the double bonds have the *E* configuration. Like rubber, gutta-percha is exuded by certain trees, but it is much less common. It is also harder and more brittle than rubber. Gutta-percha is the filling material that dentists use in root canals. At one time, it was used for the casing of golf balls. It is no longer used because it becomes brittle in cold weather and tends to split on impact.

PROBLEM 12

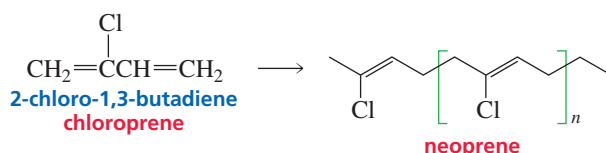
Draw a short segment of gutta-percha.

By mimicking nature, scientists have learned to make synthetic rubbers with properties tailored to meet human needs. These materials have some of the properties of natural rubber, including being waterproof and elastic, but they have some improved properties as well; they are tougher, more flexible, and more durable than natural rubber.

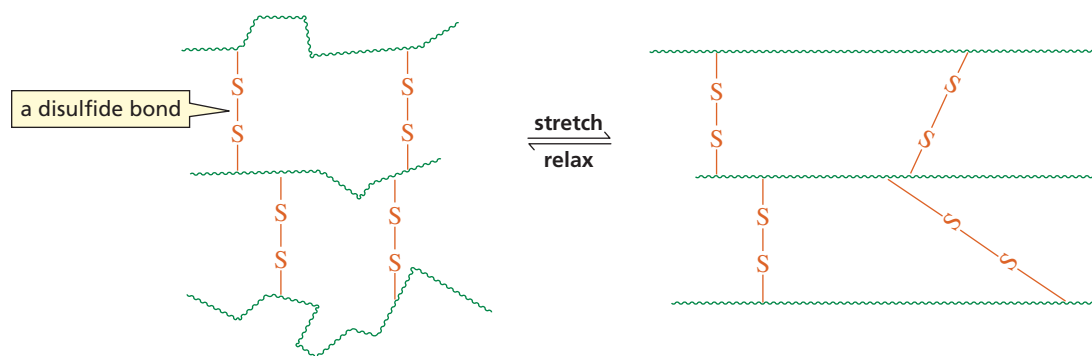
One synthetic rubber, in which all the double bonds are cis, is formed by polymerizing 1,3-butadiene.

1,3-butadiene monomers $\longrightarrow$ (*Z*)-poly(1,3-butadiene)
a synthetic rubber

Neoprene is a synthetic rubber that is made by polymerizing 2-chloro-1,3-butadiene. It is used to make wet suits, shoe soles, tires, hoses, and coated fabrics.

$CH_2{=}C(Cl)CH{=}CH_2 \longrightarrow$ neoprene

2-chloro-1,3-butadiene
chloroprene

A problem common to both natural and most synthetic rubbers is that the polymers are soft and sticky. However, they can be hardened by *vulcanization*. Charles Goodyear discovered this process while looking for ways to improve the properties of rubber. He accidentally spilled a mixture of rubber and sulfur on a hot stove. To his surprise, the mixture became hard but flexible. He called the heating of rubber with sulfur vulcanization, after Vulcan, the Roman god of fire.

Heating rubber with sulfur causes **cross-linking** of the separate polymer chains through disulfide bonds (Figure 15.1). Thus, the vulcanized chains are covalently bonded to each other in one giant molecule. Because the chains have double bonds, they have bends and kinks that allow them to stretch. When the rubber is stretched, the chains straighten out in the direction of the pull. The cross-linking prevents rubber from being torn when it is stretched; moreover, the cross-links provide a reference framework for the material to return to when the stretching force is removed.

The greater the degree of cross-linking, the more rigid is the polymer.

◀ **Figure 15.1**
The rigidity of rubber is increased by cross-linking the polymer chains with disulfide bonds. When rubber is stretched, the randomly coiled chains straighten out and orient themselves along the direction of the stretch.

The physical properties of rubber can be controlled by regulating the amount of sulfur used in vulcanization. Rubber made with 1%–3% sulfur is soft and stretchy and is used to make rubber bands. Rubber made with 3%–10% sulfur is more rigid and is used in the manufacture of tires. Goodyear's name can be found on many tires sold today. The story of rubber is an example of a scientist taking a natural material and finding ways to improve its properties for useful applications.

PROBLEM 13

a. Draw three segments of the polymer that would be formed from 1,4-polymerization of 1,3-butadiene in which all the double bonds are trans.

b. Draw three segments of the polymer that would be formed from 1,2-polymerization of 1,3-butadiene.

15.6 COPOLYMERS

The polymers we have discussed so far are **homopolymers**—they are formed from only one type of monomer. Often, two or more different monomers are used to form a **copolymer.** Increasing the number of different monomers used to form a copolymer dramatically increases the number of different copolymers that can be formed. Even if only two kinds of monomers are used, copolymers with very different properties can be prepared by varying the amounts of each monomer. Both chain-growth polymers and step-growth polymers can be copolymers. Many of the synthetic polymers used today are copolymers. Table 15.5 shows some common copolymers and the monomers from which they are synthesized.

There are several types of copolymers. In an **alternating copolymer,** the two monomers alternate. A **block copolymer** consists of blocks of each kind of monomer. A **random copolymer** has a random distribution of monomers. A **graft copolymer** contains branches derived from one monomer grafted onto a backbone derived from another monomer. These structural differences extend the range of physical properties available to the scientist designing the copolymer.

an alternating copolymer ABABABABABABABABABABABA

a block copolymer AAAAABBBBBAAAAABBBBBAAA

a random copolymer AABABABBABAABBABABBAAAB

a graft copolymer

```
AAAAAAAAAAAAAAAAAAAAAAA
   B         B         B
   B         B         B
   B         B         B
   B         B         B
   B         B         B
   B         B         B
```

Table 15.5 Some Examples of Copolymers and Their Uses

Monomers	Copolymer name	Uses
$CH_2{=}CHCl$ (vinyl chloride) + $CH_2{=}CCl_2$ (vinylidene chloride)	Saran	film for wrapping food
$CH_2{=}CH{-}C_6H_5$ (styrene) + $CH_2{=}CH{-}C{\equiv}N$ (acrylonitrile)	SAN	dishwasher-safe objects, vacuum cleaner parts
$CH_2{=}CH{-}C{\equiv}N$ (acrylonitrile) + $CH_2{=}CH{-}CH{=}CH_2$ (1,3-butadiene) + $CH_2{=}CH{-}C_6H_5$ (styrene)	ABS	bumpers, crash helmets, golf-club heads, luggage
$CH_2{=}C(CH_3)CH_3$ (isobutylene) + $CH_2{=}C(CH_3)CH{=}CH_2$ (isoprene)	butyl rubber	inner tubes, balls, inflatable sporting goods

Nanocontainers

Scientists have synthesized block copolymers that form micelles (Section 20.3). These spherical copolymers are currently being investigated for their possible use as nanocontainers (10–100 nanometers in diameter) for the delivery of non-water-soluble drugs to target cells. This strategy would allow a higher concentration of a drug to reach a cell than would occur in the natural aqueous milieu. In addition, targeting the drug to the required cells would lower the required dosage of the drug.

PROBLEM 14

Draw four segments of SAN, an alternating copolymer.

15.7 STEP-GROWTH POLYMERS

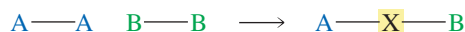
Step-growth polymers are formed by the intermolecular reaction of molecules with a functional group at each end. When the functional groups react, in most cases a small molecule such as H_2O, alcohol, or HCl is lost. This is why these polymers are also called *condensation polymers* (Section 13.6).

A step-growth polymer can be formed by the reaction of a single bifunctional compound with two different functional groups, A and B. Functional group A of one molecule reacts with functional group B of another molecule to form the compound (A—X—B) that undergoes polymerization.

$$A—B \quad A—B \longrightarrow A—X—B$$

A step-growth polymer can also be formed by the reaction of two different bifunctional compounds. One contains two A functional groups and the other contains two B functional groups. Functional group A reacts with functional group B to form the compound (A—X—B) that undergoes polymerization.

Step-growth polymers are made by combining molecules with reactive groups at each end.

$$A—A \quad B—B \longrightarrow A—X—B$$

The formation of step-growth polymers, unlike the formation of chain-growth polymers, does not occur through chain reactions. Any two monomers (or short chains) can react. The progress of a typical step-growth polymerization is shown schematically in Figure 15.2. When the reaction is 50% complete (12 bonds have formed between 25 monomers), the reaction products are primarily dimers and trimers. Even at 75% completion, no long chains have been formed. This means that if step-growth polymerization is to lead to long-chain polymers, very high yields must be achieved. We will see that the reactions involved in step-growth polymerizations are relatively simple (ester and amide formation). However, polymer chemists expend a great deal of effort to arrive at synthetic and processing methods that will result in high-molecular-weight polymers.

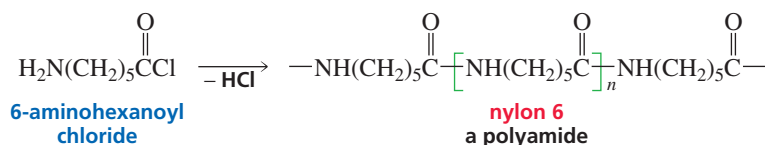
▲ **Figure 15.2**
Progress of a step-growth polymerization.

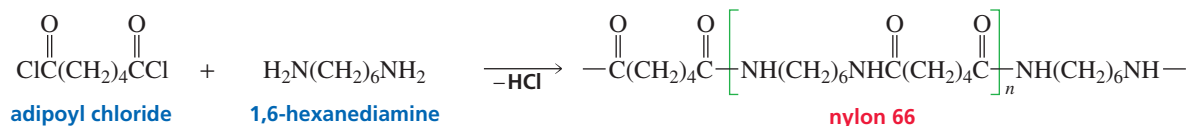
15.8 CLASSES OF STEP-GROWTH POLYMERS

Polyamides

Nylon 6 is an example of a step-growth polymer formed from a monomer with two different functional groups. The acyl chloride group of one monomer reacts with the amino group of another monomer to form an amide (Section 11.7). Thus, nylon is a **polyamide.**

This particular nylon is called nylon 6 because it is formed from the polymerization of 6-aminohexanoyl chloride, a compound that contains six carbons.

$$\underset{\textbf{6-aminohexanoyl chloride}}{H_2N(CH_2)_5\overset{O}{\overset{\|}{C}}Cl} \xrightarrow[-\,HCl]{} \underset{\textbf{nylon 6, a polyamide}}{-NH(CH_2)_5\overset{O}{\overset{\|}{C}}\left[NH(CH_2)_5\overset{O}{\overset{\|}{C}}\right]_n NH(CH_2)_5\overset{O}{\overset{\|}{C}}-}$$

A related polyamide, nylon 66, is an example of a step-growth polymer formed by two different bifunctional monomers—adipoyl chloride and 1,6-hexanediamine. It is called nylon 66 because the two starting materials each have 6 carbons.

$$\underset{\textbf{adipoyl chloride}}{Cl\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}Cl} + \underset{\textbf{1,6-hexanediamine}}{H_2N(CH_2)_6NH_2} \xrightarrow[-HCl]{} \underset{\textbf{nylon 66}}{-\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}\left[NH(CH_2)_6NH\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}\right]_n NH(CH_2)_6NH-}$$

Nylon is pulled from a beaker of adipoyl chloride and 1,6-hexanediamine.

Nylon first found wide use in textiles and carpets. Because it is resistant to stress, it is also used for such things as mountaineering ropes, tire cords, and fishing lines, and as a substitute for metal in bearings and gears. The usefulness of nylon precipitated a search for more new "super fibers" with super strength and super heat resistance.

PROBLEM 15♦

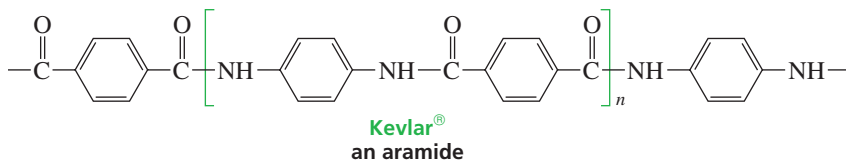
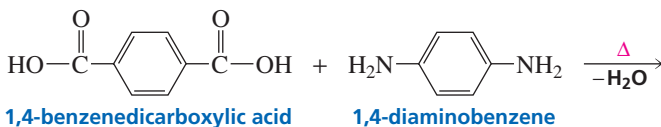
a. Draw a short segment of nylon 4. **b.** Draw a short segment of nylon 44.

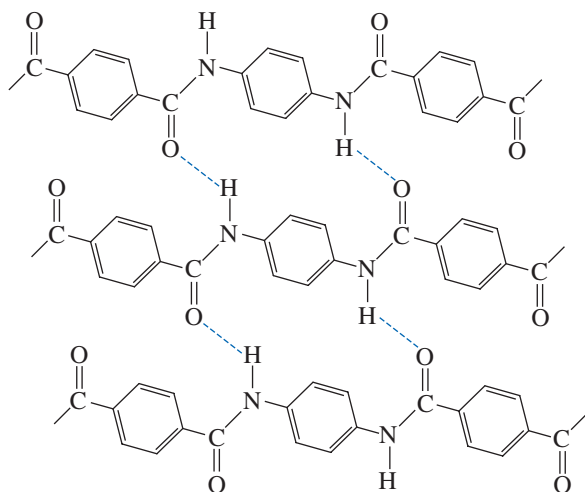
PROBLEM 16

Write an equation that explains what will happen if a scientist working in the laboratory spills an aqueous solution of sulfuric acid on her nylon 66 hose.

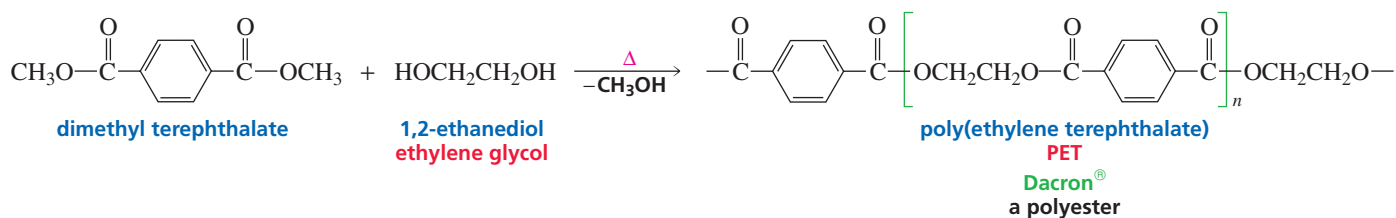
Kevlar is called a super fiber because of its strength; it is an aromatic polyamide. Aromatic polyamides are called **aramides.**

$$\underset{\textbf{1,4-benzenedicarboxylic acid}}{HO-\overset{O}{\overset{\|}{C}}-C_6H_4-\overset{O}{\overset{\|}{C}}-OH} + \underset{\textbf{1,4-diaminobenzene}}{H_2N-C_6H_4-NH_2} \xrightarrow[-H_2O]{\Delta}$$

$$\underset{\textbf{Kevlar® an aramide}}{-\overset{O}{\overset{\|}{C}}-C_6H_4-\overset{O}{\overset{\|}{C}}\left[NH-C_6H_4-NH-\overset{O}{\overset{\|}{C}}-C_6H_4-\overset{O}{\overset{\|}{C}}\right]_n NH-C_6H_4-NH-}$$

nylon rope

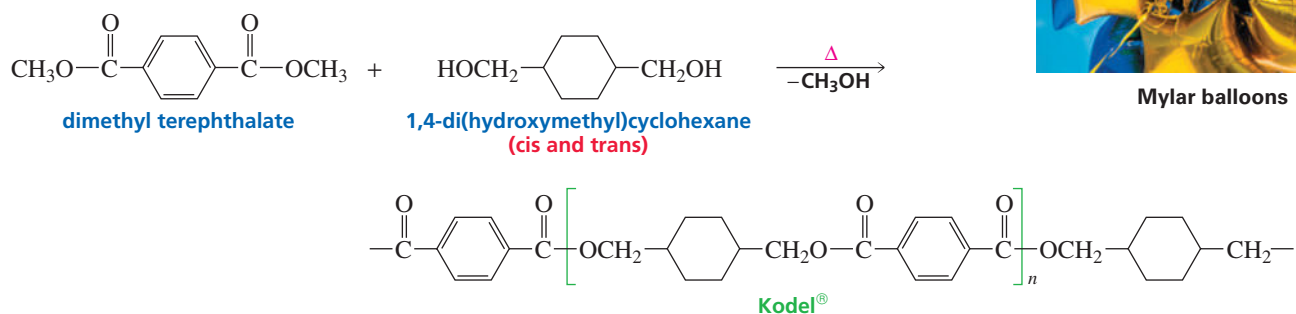
Kevlar owes its strength to the way the individual polymer chains interact with each other. The chains are hydrogen bonded, forming a sheet-like structure. Kevlar is five times stronger than steel on an equal weight basis. Army helmets are made of Kevlar, which is also used for lightweight bullet-resistant vests, automobile parts, high-performance skis, the ropes used on the Mars Pathfinder, and high-performance sails used in the America's Cup. Because it is stable at very high temperatures, it is used in the protective clothing worn by firefighters.

Polyesters

Dacron is the most common of the group of step-growth polymers known as **polyesters**—polymers containing many ester groups. Polyesters are used for clothing and are responsible for the wrinkle-resistant behavior of many fabrics. Dacron is made by the transesterification of dimethyl terephthalate with ethylene glycol (Section 11.8). The durability and moisture resistance of this polymer contribute to its "wash-and-wear" characteristics. Because PET is lightweight, it is also used for transparent soft drink bottles.

dimethyl terephthalate + 1,2-ethanediol (ethylene glycol) $\xrightarrow[-CH_3OH]{\Delta}$ poly(ethylene terephthalate) PET Dacron® a polyester

Poly(ethylene terephthlate) can also be processed to form a film known as Mylar. Mylar is tear resistant and, when processed, has a tensile strength nearly as great as that of steel. It is used in the manufacture of magnetic recording tape and sails. Aluminized Mylar was used to make the Echo satellite that was put into orbit around Earth as a giant reflector of microwave signals.

Kodel polyester also is formed by a transesterification reaction. The stiff polyester chain causes the fiber to have a harsh feel that can be softened by blending it with wool or cotton.

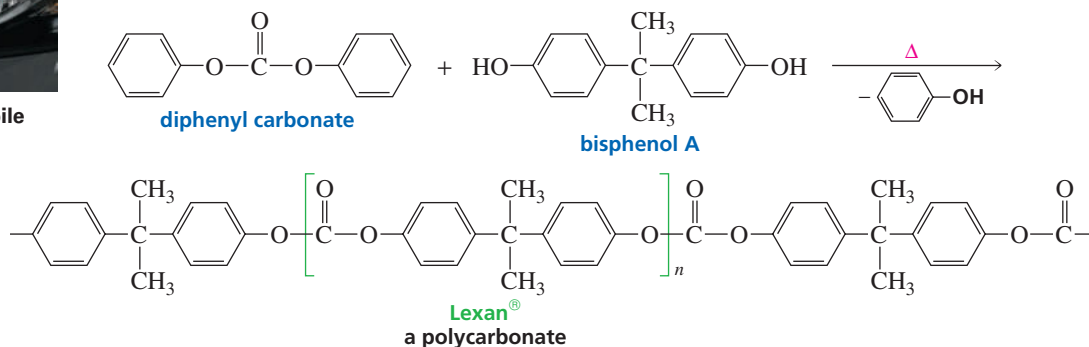
Mylar balloons

dimethyl terephthalate + 1,4-di(hydroxymethyl)cyclohexane (cis and trans) $\xrightarrow[-CH_3OH]{\Delta}$ Kodel®

PROBLEM 17

What happens to polyester slacks if aqueous NaOH is spilled on them?

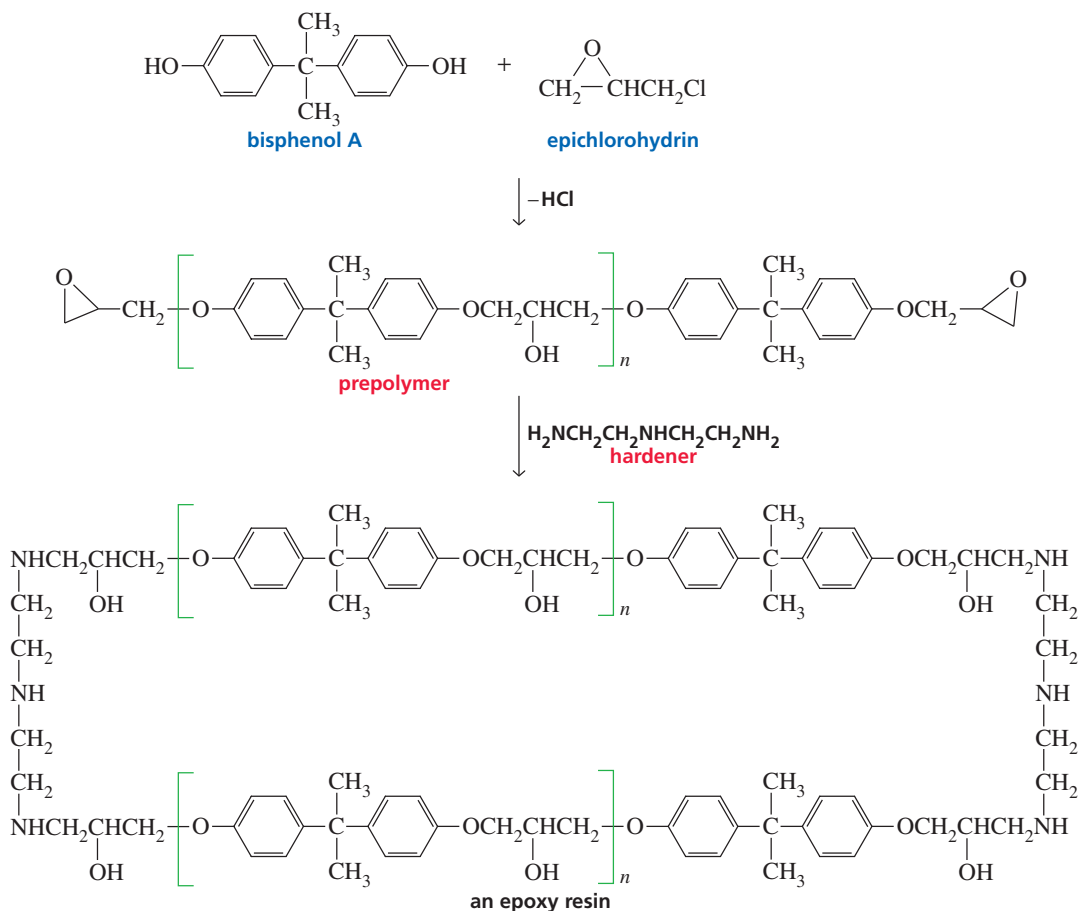
Lexan lens in an automobile

Polyesters with two OR groups bonded to the same carbon are known as **polycarbonates.** Lexan, a polycarbonate produced by the transesterification of diphenyl carbonate with bisphenol A, is a strong, transparent polymer used for motor vehicle headlight lenses, bullet-proof windows, and traffic-light lenses. In recent years, polycarbonates have become important in the automobile industry as well as in the manufacture of compact discs.

diphenyl carbonate + bisphenol A $\xrightarrow{\Delta}$ (− phenol) Lexan®, a polycarbonate

Epoxy Resins

Epoxy resins are the strongest adhesives known; they are extensively cross-linked systems. They can adhere to almost any surface and are resistant to solvents and to extremes of temperature. Epoxy cement is purchased as a kit consisting of a low-molecular-weight *prepolymer* (the most common is a copolymer of bisphenol A and epichlorohydrin) and a *hardener* that react when mixed to form a cross-linked polymer.

bisphenol A + epichlorohydrin (CH_2—$CHCH_2Cl$ epoxide) $\xrightarrow{-HCl}$ prepolymer

prepolymer $\xrightarrow{H_2NCH_2CH_2NHCH_2CH_2NH_2 \text{ (hardener)}}$ an epoxy resin

Health Concerns: Bisphenol A and Phthalates

Animal studies have raised concerns about human exposure to bisphenol A and phthalates. Pregnant rats exposed to bisphenol A have been found to have a three to four times higher incidence of precancerous lesions in their mammary ducts. Bisphenol A (BPA) is used in the manufacture of polycarbonates and epoxy resins. Although there is no evidence that bisphenol A has an adverse impact on humans, most manufacturers of polycarbonates have stopped using the compound, and BPA-free water bottles are now found in stores.

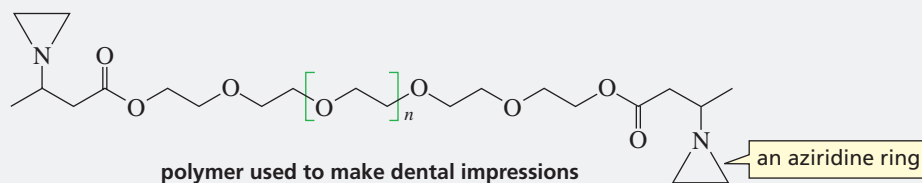
Phthalates have been found to be endocrine disruptors—that is, they can alter the proper balance of hormones. Therefore, the primary risk they pose is to a developing fetus. It is difficult to avoid phthalates because of the numerous items (for example, the linings of most aluminum food and beverage cans) that contain them.

Designing a Polymer

Today, polymers are being designed to meet ever more exacting and specific needs. A polymer used for making dental impressions, for example, must be soft enough initially to be molded around the teeth but must become hard enough later to maintain a fixed shape.

The polymer commonly used for dental impressions contains three-membered aziridine rings that react to form cross-links between the chains. Because aziridine rings are not very reactive, cross-linking occurs relatively slowly, so most of the hardening of the polymer does not occur until the polymer is removed from the patient's mouth.

an aziridine ring

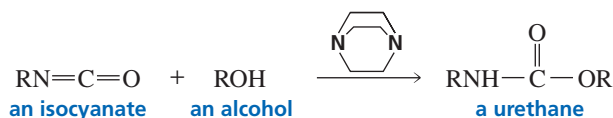
polymer used to make dental impressions

PROBLEM 18

a. Propose a mechanism for the formation of the prepolymer formed by bisphenol A and epichlorohydrin.

b. Propose a mechanism for the reaction of the prepolymer with the hardener.

Polyurethanes

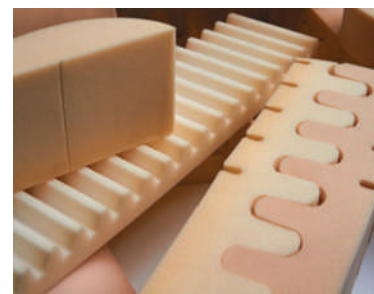
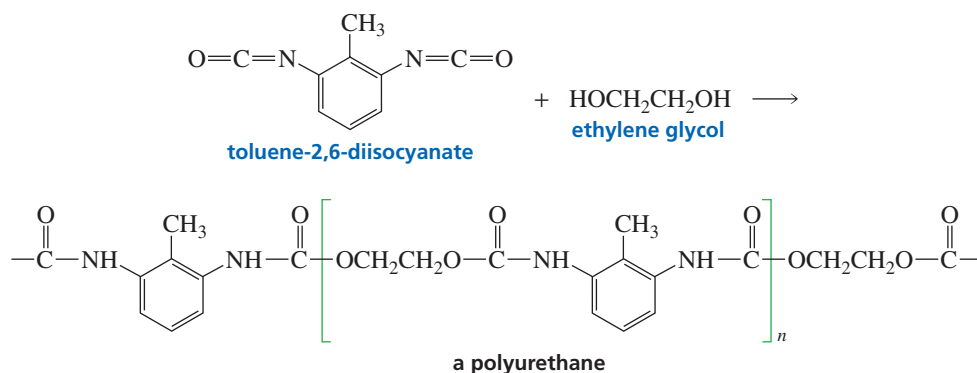
A **urethane**—also called a carbamate—is a compound that has an OR group and an NHR group bonded to the same carbonyl carbon. Urethanes can be prepared by treating an isocyanate with an alcohol, in the presence of a catalyst such as a tertiary amine.

$$\underset{\text{an isocyanate}}{RN{=}C{=}O} + \underset{\text{an alcohol}}{ROH} \longrightarrow \underset{\text{a urethane}}{RNH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR}$$

One of the most common **polyurethanes**—polymers that contain urethane groups—is prepared by the polymerization of toluene-2,6-diisocyanate and ethylene glycol. If the reaction is carried out in the presence of a blowing agent, the product is a polyurethane foam. Blowing agents are gases such as nitrogen or carbon dioxide. Polyurethane foams are used for furniture stuffing, bedding, carpet backings, and insulation. Notice that polyurethanes prepared from diisocyanates and diols are the only step-growth polymers we have seen in which a small molecule is not lost during polymerization.

polyurethane foam

$$O{=}C{=}N\text{-}C_6H_3(CH_3)\text{-}N{=}C{=}O \;+\; HOCH_2CH_2OH \longrightarrow$$

toluene-2,6-diisocyanate   ethylene glycol

$$\text{—}\overset{O}{\overset{\|}{C}}\text{—NH—}C_6H_3(CH_3)\text{—NH—}\overset{O}{\overset{\|}{C}}\left[\text{—OCH}_2\text{CH}_2\text{O—}\overset{O}{\overset{\|}{C}}\text{—NH—}C_6H_3(CH_3)\text{—NH—}\overset{O}{\overset{\|}{C}}\right]_n\text{—OCH}_2\text{CH}_2\text{O—}\overset{O}{\overset{\|}{C}}\text{—}$$

a polyurethane

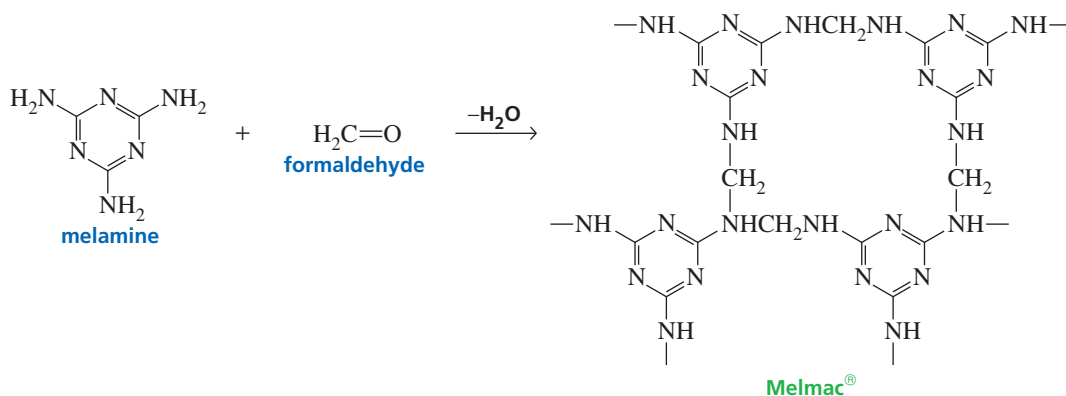
One of the most important uses of polyurethanes is in fabrics with elastic properties, such as Lycra—known generically as spandex. These fabrics are block copolymers in which some of the polymer segments are polyurethanes, some are polyesters, and some are polyethers; they are always blended with cotton or wool. The blocks of polyurethane are rigid and short, enabling it to be a fabric; the blocks of polyesters and polyethers are flexible and long, providing the elastic properties. When stretched, the soft blocks, which are cross-linked by the hard blocks, become highly ordered. When the tension is released, they revert to their previous state.

Cross-Linked Polymers

Very rigid materials can be obtained if the polymer chains are cross-linked. The greater the degree of cross-linking, the more rigid is the polymer. After they are hardened, they cannot be remelted by heating because the cross-links are covalent bonds, not van der Waals forces. Crosslinking reduces the mobility of the polymer chains, causing the polymer to be relatively brittle.

Melmac, a highly cross-linked polymer of melamine and formaldehyde, is a hard, moisture-resistant material. Because it is colorless, Melmac can be made into materials with pastel colors. It is used to make counter surfaces and lightweight dishes.

$$\text{melamine} + H_2C{=}O \xrightarrow{-H_2O} \text{Melmac}^{®}$$

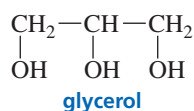
melamine   formaldehyde   Melmac®

PROBLEM 19

Propose a mechanism for the formation of Melmac.

PROBLEM 20

Explain why, when a small amount of glycerol is added to the reaction mixture of toluene-2,6-diisocyanate and ethylene glycol during the synthesis of polyurethane foam, a much stiffer foam is obtained.

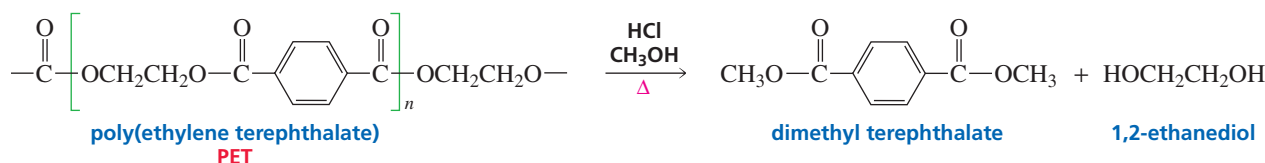
$$\underset{OH}{\underset{|}{CH_2}}\text{—}\underset{OH}{\underset{|}{CH}}\text{—}\underset{OH}{\underset{|}{CH_2}}$$

glycerol

15.9 RECYCLING POLYMERS

We saw in Section 15.2 that polymers are assigned a number from 1 to 6 that indicates the ease with which that kind of polymer can be recycled—the lower the number, the easier it can be recycled. Unfortunately, only polymers with the two lowest numbers PET (1)—the polymer used to make soft drink bottles—and HDPE (2)—the denser polymer used for juice and milk bottles—are recycled to any significant extent. This amounts to less than 25% of all polymers. The others are found in landfills.

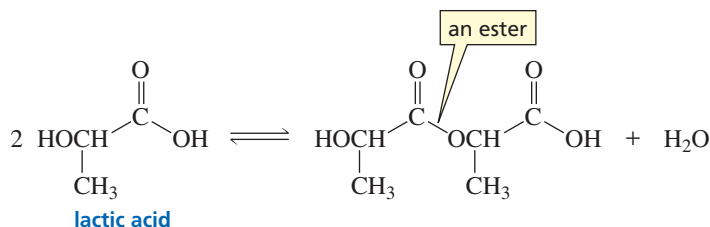
PET is recycled by heating the polymer in an acidic solution of methanol. This transesterification reaction (Section 11.8) is the reverse of the transesterifcation reaction that formed the polymer (page 545). Because the products of recycling PET are the monomers used to make it, the products are recycled to make more PET.

$$-\overset{O}{\overset{\|}{C}}-\left[OCH_2CH_2O-\overset{O}{\overset{\|}{C}}-C_6H_4-\overset{O}{\overset{\|}{C}}\right]_n-OCH_2CH_2O- \xrightarrow[\Delta]{HCl,\ CH_3OH} CH_3O-\overset{O}{\overset{\|}{C}}-C_6H_4-\overset{O}{\overset{\|}{C}}-OCH_3 + HOCH_2CH_2OH$$

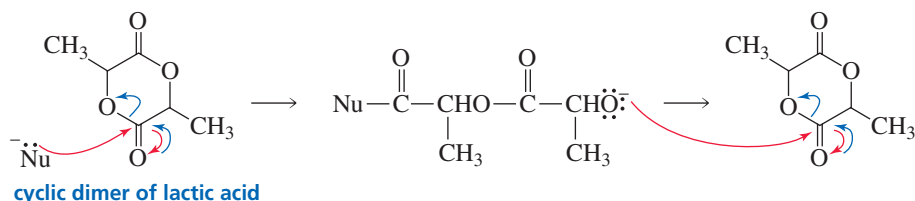
poly(ethylene terephthalate) PET — dimethyl terephthalate — 1,2-ethanediol

15.10 BIODEGRADABLE POLYMERS

Biodegradable polymers are polymers that can be degraded by microorganisms such as bacteria, fungi, or algae. Polylactide (PLA), a biodegradable polymer of lactic acid, has found wide use. When lactic acid is polymerized, a molecule of water is lost that can hydrolyze the new ester bond, reforming lactic acid.

$$2\ HOCH(CH_3)\overset{O}{\overset{\|}{C}}OH \rightleftharpoons HOCH(CH_3)\overset{O}{\overset{\|}{C}}OCH(CH_3)\overset{O}{\overset{\|}{C}}OH + H_2O$$

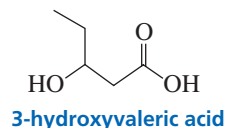
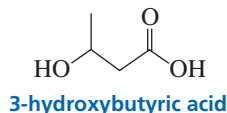
lactic acid; an ester

However, if lactic acid is converted to a cyclic dimer, the dimer can form a polymer without the loss of water by ring-opening polymerization. (The red arrows show formation of the tetrahedral intermediate; the blue arrows show the subsequent elimination from the tetrahedral intermediate.)

$$\text{cyclic dimer of lactic acid} + {}^-\!:Nu \longrightarrow Nu-\overset{O}{\overset{\|}{C}}-\underset{CH_3}{CH}-O-\overset{O}{\overset{\|}{C}}-\underset{CH_3}{CH}-\ddot{O}:^- \longrightarrow \text{(attacks another cyclic dimer)}$$

cyclic dimer of lactic acid

Because lactic acid has an asymmetric center, there are several different forms of the polymer. The polymer's physical properties depend on the ratio of *R* and *S* enantiomers used in its synthesis. Polylactides are currently being used in nonwrinkle fabrics, microwavable trays, food packaging, and in several medical applications such as sutures, stents, and drug-delivery devices. They are also used for cold drink glasses. Unfortunately, hot drinks cause the polymer to liquify. Although polylactides are more expensive than nonbiodegradable polymers, their price is falling as their production increases.

glasses made of PLA

Polyhydroxyalkanoates (PHAs) are also biodegradable polymers. These are step-growth polymers of 3-hydroxycarboxylic acids. Thus, like PLA, they are polyesters. The most common PHA is PHB, a polymer of 3-hydroxybutyric acid; it can be used for many of the things that polypropylene is now used for. Unlike polypropylene, which

floats, PHB sinks. PHBV, a PHA marketed under the trade name Biopol, is a copolymer of 3-hydroxybutyric acid and 3-hydroxyvaleric acid. It is being used for such things as wastepaper baskets, toothbrush holders, and soap dispensers. PHAs are degraded by bacteria to CO_2 and H_2O.

HO OH O — 3-hydroxybutyric acid

HO OH O — 3-hydroxyvaleric acid

PROBLEM 21

a. Draw the structure of a short segment of PHB.
b. Draw the structure of a short segment of PHBV with alternating monomers.

SOME IMPORTANT THINGS TO REMEMBER

- A **polymer** is a giant molecule made by covalently linking repeating units of small molecules called **monomers.** The process of linking them is called **polymerization.**
- Polymers can be divided into two groups: **synthetic polymers,** which are synthesized by scientists, and **biopolymers,** which are synthesized by cells.
- Synthetic polymers can be divided into two classes: **chain-growth polymers** and **step-growth polymers.**
- Chain-growth polymers are made by **chain reactions,** which add monomers to the end of a growing chain.
- The chain reactions take place by one of three mechanisms: **radical polymerization, cationic polymerization,** or **anionic polymerization.**
- Each mechanism has an initiation step that starts the polymerization, propagation steps that allow the chain to grow at the **propagating site,** and termination steps that stop the growth of the chain.
- The choice of mechanism depends on the structure of the **monomer** and the initiator used to activate the monomer.
- In radical polymerization, the initiator is a radical; in cationic polymerization, it is an electrophile; and in anionic polymerization, it is a nucleophile.
- Chain-growth polymerization exhibits a preference for **head-to-tail addition.**
- Branching affects the physical properties of the polymer because unbranched chains can pack together more closely than branched chains can.
- Nonterminated polymer chains are called **living polymers.**
- The substituents are on the same side of the carbon chain in an **isotactic polymer,** alternate on both sides of the chain in a **syndiotactic polymer,** and are randomly oriented in an **atactic polymer.**
- The structure of a polymer can be controlled with **Ziegler–Natta catalysts.**
- Natural rubber is a polymer of 2-methyl-1,3-butadiene. Synthetic rubbers have been made by polymerizing dienes other than 2-methyl-1,3-butadiene.
- Heating rubber with sulfur to cross-link the chains is called **vulcanization.**
- **Homopolymers** are made of one kind of monomer; **copolymers** are made of more than one kind.
- **Step-growth polymers** are made by combining two molecules with reactive functional groups at each end.
- Nylon is a **polyamide. Aramides** are aromatic polyamides. Dacron is a **polyester.**
- **Polycarbonates** have two alkoxy groups bonded to the same carbonyl carbon. A **urethane** is a compound that has an OR and an NHR group bonded to the same carbonyl carbon.
- The greater the degree of cross-linking, the more rigid the polymer.
- **Biodegradable polymers** can be degraded by microorganisms.

PROBLEMS

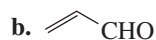
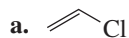
22. Draw short segments of the polymers obtained from the following monomers. In each case, indicate whether the polymerization is a chain-growth or a step-growth polymerization.

a. $CH_2{=}CHCl$ (vinyl chloride, drawn as skeletal structure with Cl)

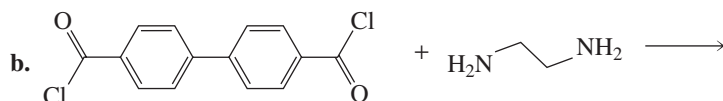
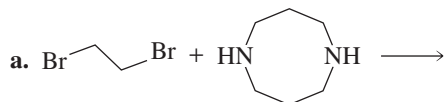
b. $CH_2{=}CHCHO$ (drawn as skeletal structure with CHO)

c. $H_2N(CH_2)_3COCl$

d. $ClC(=O)(CH_2)_5C(=O)Cl$ + $HO(CH_2)_3OH$

e. $OCN{-}CH_2CH_2{-}NCO$ + $HO(CH_2)_3OH$

23. Draw the repeating unit of the step-growth polymer that will be formed from each of the following pairs of monomers:

a. $BrCH_2CH_2CH_2Br$ + HN (cyclic diamine ring) NH ⟶

b. 4,4′-biphenyldicarbonyl chloride (O, Cl / Cl, O) + $H_2NCH_2CH_2NH_2$ ⟶

24. Draw the structure of the monomer or monomers used to synthesize the following polymers, and indicate whether each is a chain-growth polymer or a step-growth polymer.

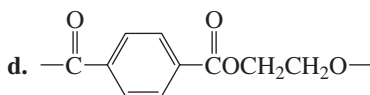
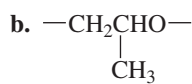
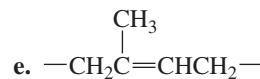
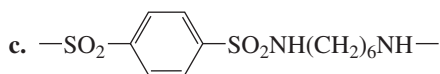
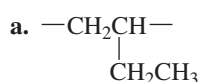
a. $-CH_2CH(CH_2CH_3)-$

b. $-CH_2CH(CH_3)O-$

c. $-SO_2-C_6H_4-SO_2NH(CH_2)_6NH-$

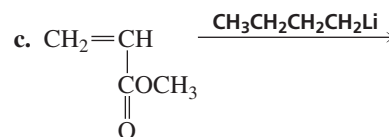
d. $-C(=O)-C_6H_4-C(=O)OCH_2CH_2O-$

e. $-CH_2C(CH_3){=}CHCH_2-$

f. $-CH_2CH_2CH_2CH_2CH_2C(=O)O-$

25. Draw short segments of the polymers obtained from the following compounds under the given reaction conditions:

a. $H_2C-CHCH_3$ (epoxide, bridged by O) $\xrightarrow{CH_3O^-}$

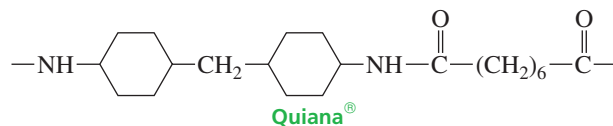
b. $CH_2{=}CHOCH_3$ $\xrightarrow{BF_3,\ H_2O}$

c. $CH_2{=}CH-C(=O)OCH_3$ $\xrightarrow{CH_3CH_2CH_2CH_2Li}$

26. A chemist carried out two polymerization reactions. One flask contained a monomer that polymerizes by a chain-growth mechanism, and the other flask contained a monomer that polymerizes by a step-growth mechanism. When the reactions were terminated early in the process and the contents of the flasks analyzed, it was found that one flask contained a high-molecular-weight polymer and very little material of intermediate molecular weight. The other contained mainly material of intermediate molecular weight and very little high-molecular-weight material. Which flask contained which product? Explain.

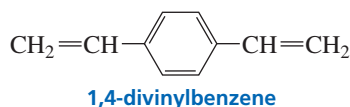
27. Quiana is a synthetic fabric that feels very much like silk.

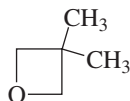
a. Is Quiana a nylon or a polyester? **b.** What monomers are used to synthesize it?

$-NH-C_6H_{10}-CH_2-C_6H_{10}-NH-C(=O)-(CH_2)_6-C(=O)-$

Quiana®

28. If a peroxide is added to styrene, the polymer known as polystyrene is formed. If a small amount of 1,4-divinylbenzene is added to the reaction mixture, a stronger and more rigid polymer is formed. Draw a short section of this more rigid polymer.

$CH_2{=}CH-C_6H_4-CH{=}CH_2$

1,4-divinylbenzene

29. A particularly strong and rigid polyester used for electronic parts is marketed under the trade name Glyptal. It is a polymer of terephthalic acid and glycerol. Draw a segment of the polymer and explain why it is so strong.

30. Draw a short segment of the polymer formed from cationic polymerization of 3,3-dimethyloxacyclobutane.

3,3-dimethyloxacyclobutane

31. Which monomer would give a greater yield of polymer: 5-hydroxypentanoic acid or 6-hydroxyhexanoic acid? Explain your choice.

32. When acrylic acid undergoes chain growth cationic polymerization, a polymer with two types of repeating units is obtained. Draw the structures of the repeating units.

COOH

acrylic acid

33. Why do vinyl raincoats become brittle as they get old, even if they are not exposed to air or to any pollutants?

34. An alternating copolymer of styrene and vinyl acetate can be turned into a graft copolymer by hydrolyzing it and then adding ethylene oxide. Draw the structure of the graft copolymer.

35. How could head-to-head poly(vinyl bromide) be synthesized?

$$-CH_2\underset{Br}{\underset{|}{C}}H\underset{Br}{\underset{|}{C}}HCH_2CH_2\underset{Br}{\underset{|}{C}}H\underset{Br}{\underset{|}{C}}HCH_2-$$

head-to-head poly(vinyl bromide)

36. Delrin (polyoxymethylene) is a tough self-lubricating polymer used in gear wheels. It is made by polymerizing formaldehyde in the presence of an acid catalyst.

a. Propose a mechanism for formation of a segment of the polymer.

b. Is Delrin a chain-growth polymer or a step-growth polymer?

16 The Organic Chemistry of Carbohydrates

a field of sugar cane

BIOORGANIC COMPOUNDS ARE ORGANIC COMPOUNDS FOUND IN LIVING SYSTEMS. The first group of bioorganic compounds we will look at are carbohydrates—the most abundant class of compounds in the biological world, making up more than 50% of the dry weight of the Earth's biomass. Carbohydrates are important constituents of all living organisms and have a variety of different functions. Some are important structural components of cells; others act as recognition sites on cell surfaces. For example, the first event in our lives was a sperm cell recognizing a carbohydrate on the outer surface of an egg. Other carbohydrates serve as a major source of metabolic energy. The leaves, fruits, seeds, stems, and roots of plants, for instance, contain carbohydrates that plants use for their own metabolic needs and these also serve the metabolic needs of the animals that eat them.

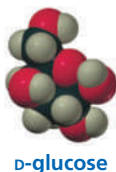
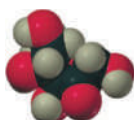
The structures of **bioorganic compounds** can be quite complex, yet their reactivity is governed by the same principles that govern the reactivity of the comparatively simple organic molecules we have discussed so far. In other words, the organic reactions that chemists carry out in the laboratory are in many ways just like those performed by nature inside a cell. Thus, bioorganic reactions can be thought of as organic reactions that take place in tiny flasks called cells.

D-glucose

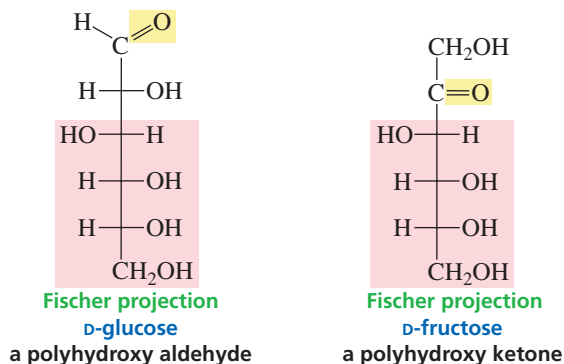
D-fructose

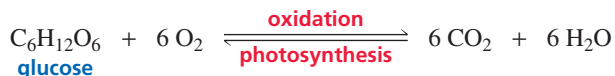
Although most bioorganic compounds have more complicated structures than those of the organic compounds you are now used to seeing, do not let the structures fool you into thinking that their chemistry must be equally complicated. One reason the structures of bioorganic compounds are more complicated is that they must be able to recognize each other. Much of their structure is for that very purpose, a function called **molecular recognition.**

Carbohydrates are polyhydroxy aldehydes such as glucose, polyhydroxy ketones such as fructose, and compounds such as sucrose formed by linking polyhydroxy aldehydes or polyhydroxy ketones together (Section 16.9).

The chemical structures of carbohydrates are commonly represented by Fischer projections. A Fischer projection represents an asymmetric center as the point of intersection of two perpendicular lines. Horizontal lines represent the bonds that project out of the

plane of the paper toward the viewer, and vertical lines represent the bonds that extend back from the plane of the paper away from the viewer. Notice that the structures of glucose and fructose differ only at the top two carbons.

All the horizontal bonds in Fischer projections point toward the viewer.

D-glucose	D-fructose
H–C=O	CH_2OH
H—OH	C=O
HO—H	HO—H
H—OH	H—OH
H—OH	H—OH
CH_2OH	CH_2OH
Fischer projection	Fischer projection
D-glucose	D-fructose
a polyhydroxy aldehyde	a polyhydroxy ketone

The most abundant carbohydrate in nature is glucose (also called dextrose on some food labels). Animals obtain glucose from food that contains glucose, such as plants. Plants produce glucose by *photosynthesis*. During photosynthesis, plants take up water through their roots and use carbon dioxide from the air to synthesize glucose and oxygen.

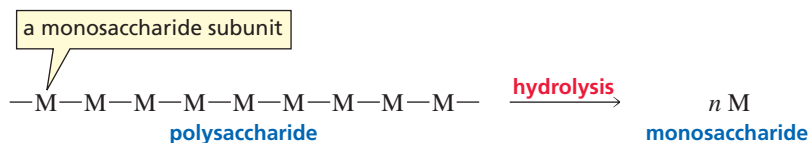
$$\underset{\text{glucose}}{C_6H_{12}O_6} + 6\,O_2 \underset{\text{photosynthesis}}{\overset{\text{oxidation}}{\rightleftharpoons}} 6\,CO_2 + 6\,H_2O$$

Since photosynthesis is the reverse of the process used by organisms to obtain energy—specifically, the oxidation of glucose to carbon dioxide and water—plants require energy to carry out photosynthesis. They obtain that energy from sunlight, which is captured by chlorophyll molecules in green plants. Photosynthesis uses the CO_2 that animals exhale as waste and generates the O_2 that animals inhale to sustain life. Nearly all the oxygen in the atmosphere has been released by photosynthetic processes.

16.1 CLASSIFICATION OF CARBOHYDRATES

The terms *carbohydrate, saccharide,* and *sugar* are used interchangeably. *Saccharide* comes from the word for sugar in several early languages (*sarkara* in Sanskrit, *sakcharon* in Greek, and *saccharum* in Latin).

Simple carbohydrates are **monosaccharides** (single sugars); **complex carbohydrates** contain two or more monosaccharides linked together. **Disaccharides** have two monosaccharides linked together, **oligosaccharides** have 3 to 10 (*oligos* is Greek for "few"), and **polysaccharides** have 10 or more. Disaccharides, oligosaccharides, and polysaccharides can be broken down to monosaccharides by hydrolysis.

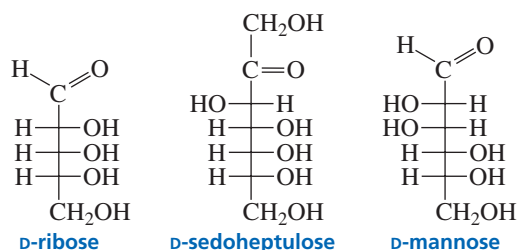
a monosaccharide subunit

$$\underset{\text{polysaccharide}}{\text{—M—M—M—M—M—M—M—M—M—}} \xrightarrow{\text{hydrolysis}} \underset{\text{monosaccharide}}{n\,\text{M}}$$

A *monosaccharide* can be a polyhydroxy aldehyde such as glucose or a polyhydroxy ketone such as fructose. Polyhydroxy aldehydes are called **aldoses** ("ald" is for aldehyde; "ose" is the suffix for a sugar); polyhydroxy ketones are called **ketoses.**

Monosaccharides are also classified according to the number of carbons they contain: those with three carbons are **trioses,** those with four carbons are **tetroses,** those with five carbons are **pentoses,** and those with six and seven carbons are **hexoses** and **heptoses.** Therefore, a six-carbon polyhydroxy aldehyde such as glucose is an aldohexose, whereas a six-carbon polyhydroxy ketone such as fructose is a ketohexose.

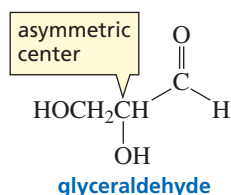
PROBLEM 1♦

Classify the following monosaccharides:

D-ribose D-sedoheptulose D-mannose

16.2 THE D AND L NOTATIONS

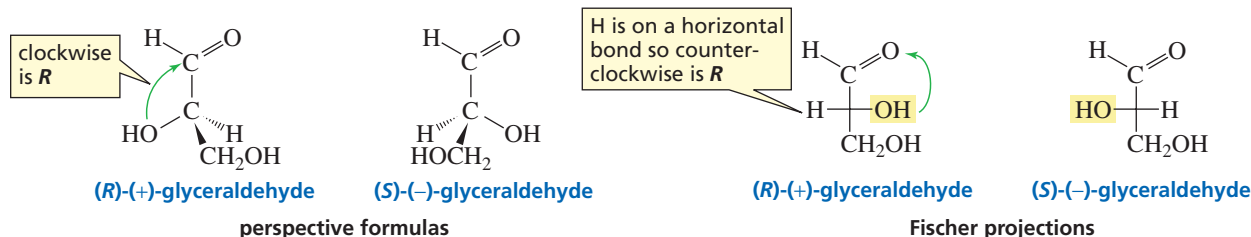
The smallest aldose, and the only one whose name does not end in "ose," is glyceraldehyde, an aldotriose.

asymmetric center

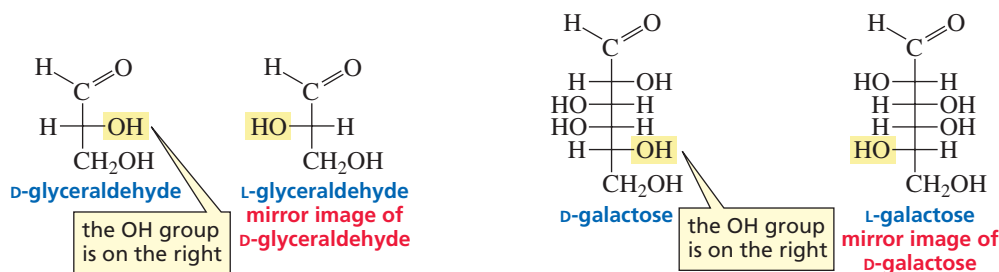
$HOCH_2CH(OH)CHO$

glyceraldehyde

A carbon to which four different groups are attached is an asymmetric center.

Because glyceraldehyde has an asymmetric center, it can exist as a pair of enantiomers. We know that the isomer below on the left has the *R* configuration because an arrow drawn from the highest priority substituent (OH) to the next highest priority substituent (HC=O) is clockwise and the lowest priority group is on a hatched wedge (Section 4.7). The *R* and *S* enantiomers drawn as Fischer projections are shown on the right.

perspective formulas Fischer projections

The notations D and L are used to describe the configurations of carbohydrates. In a Fischer projection of a monosaccharide, the carbonyl group is always placed on top (in the case of aldoses) or as close to the top as possible (in the case of ketoses). Examine the Fischer projection of galactose shown below and note that the compound has four asymmetric centers (C-2, C-3, C-4, and C-5). *If the OH group attached to the bottommost asymmetric center (the second carbon from the bottom) is on the right, then the compound is a D-sugar. If that same OH group is on the left, then the compound is an L-sugar.* Almost all sugars found in nature are D-sugars. The mirror image of a D-sugar is an L-sugar.

To determine the configuration of a Fischer projection, draw an arrow from the highest priority to the next highest priority.

If the arrow is counterclockwise, the configuration is *R* if the lowest priority substituent is on a horizontal bond and *S* if it is on a vertical bond.

If the arrow is clockwise, the configuration is *S* if the lowest priority is on a horizontal bond and *R* if it is on a vertical bond.

D-glyceraldehyde — the OH group is on the right

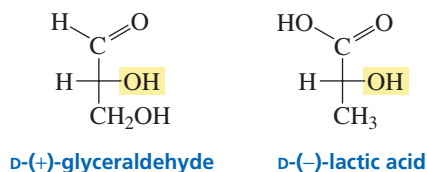
L-glyceraldehyde — mirror image of D-glyceraldehyde

D-galactose — the OH group is on the right

L-galactose — mirror image of D-galactose

The common name of the monosaccharide, together with the D or L designation, completely defines its structure, because the configurations of all the asymmetric centers are implicit in the common name. Thus, the structure of L-galactose is obtained by changing the configuration of all the asymmetric centers in D-galactose.

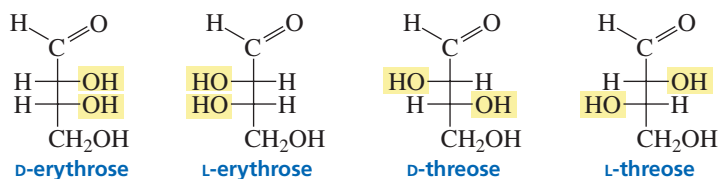
Like *R* and *S*, the symbols D and L describe the configuration of a compound but do not indicate whether the compound rotates the plane of polarization of polarized light to the right (+) or to the left (−) (Section 4.8). For example, D-glyceraldehyde is dextrorotatory, whereas D-lactic acid is levorotatory. In other words, optical rotation, like a melting point or a boiling point, is a physical property of a compound, whereas "*R*, *S*, D, and L" are conventions humans use to indicate configuration.

D-(+)-glyceraldehyde D-(−)-lactic acid

PROBLEM 2

Draw Fischer projections of L-glucose and L-fructose.

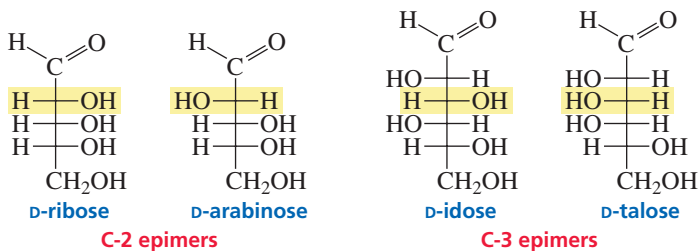
16.3 THE CONFIGURATIONS OF ALDOSES

Aldotetroses have two asymmetric centers and, therefore, four stereoisomers. Two of the stereoisomers are D-sugars and two are L-sugars.

D-erythrose L-erythrose D-threose L-threose

Aldopentoses have three asymmetric centers and, therefore, eight stereoisomers (four pairs of enantiomers); aldohexoses have four asymmetric centers and 16 stereoisomers (eight pairs of enantiomers). The structures and names of the four D-aldopentoses and the eight D-aldohexoses are shown in Table 16.1.

Diastereomers are stereoisomers that are not enantiomers.

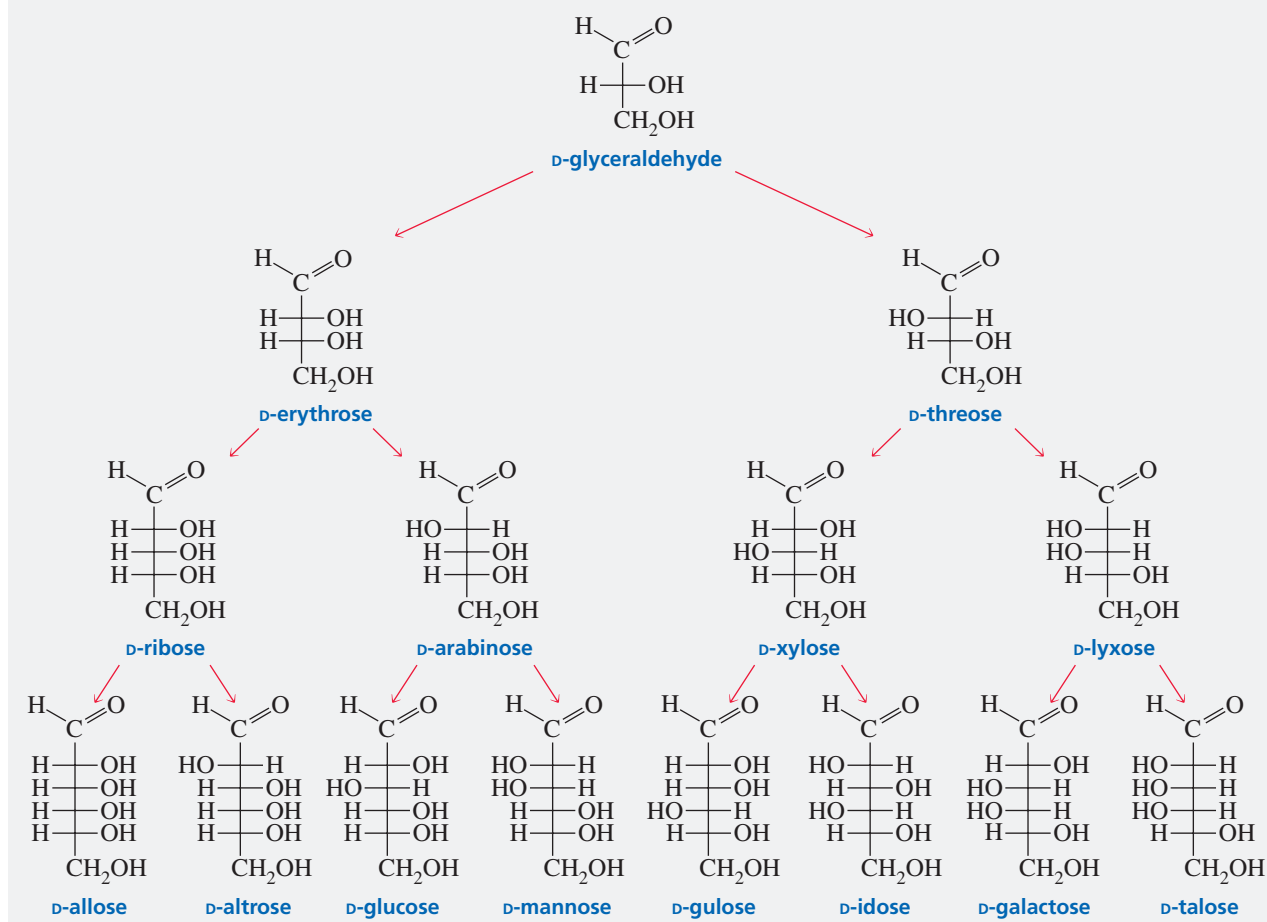
Diastereomers that differ in configuration at only one asymmetric center are called **epimers.** For example, D-ribose and D-arabinose are C-2 epimers because they differ in configuration only at C-2; D-idose and D-talose are C-3 epimers. (Recall that diastereomers are stereoisomers that are not enantiomers; Section 4.10.)

D-ribose D-arabinose D-idose D-talose

C-2 epimers C-3 epimers

D-Mannose is the C-2 epimer of D-glucose.

D-Galactose is the C-4 epimer of D-glucose.

D-Glucose, D-mannose, and D-galactose are the most common aldohexoses in living systems. An easy way to learn their structures is to memorize the structure of D-glucose and then remember that D-mannose is the C-2 epimer of D-glucose and D-galactose is the C-4 epimer of D-glucose.

Table 16.1 Configurations of the D-Aldoses

PROBLEM 3♦

a. Are D-erythrose and L-erythrose enantiomers or diastereomers?
b. Are L-erythrose and L-threose enantiomers or diastereomers?

PROBLEM 4♦

a. What sugar is the C-3 epimer of D-xylose?
b. What sugar is the C-5 epimer of D-allose?
c. What sugar is the C-4 epimer of L-gulose?
d. What sugar is the C-4 epimer of D-lyxose?

16.4 THE CONFIGURATIONS OF KETOSES

The structures of the naturally occurring ketoses are shown in Table 16.2. They all have a keto group in the 2-position. A ketose has one less asymmetric center than an aldose with the same number of carbons. Therefore, a ketose has only half as many stereoisomers as an aldose with the same number of carbons.

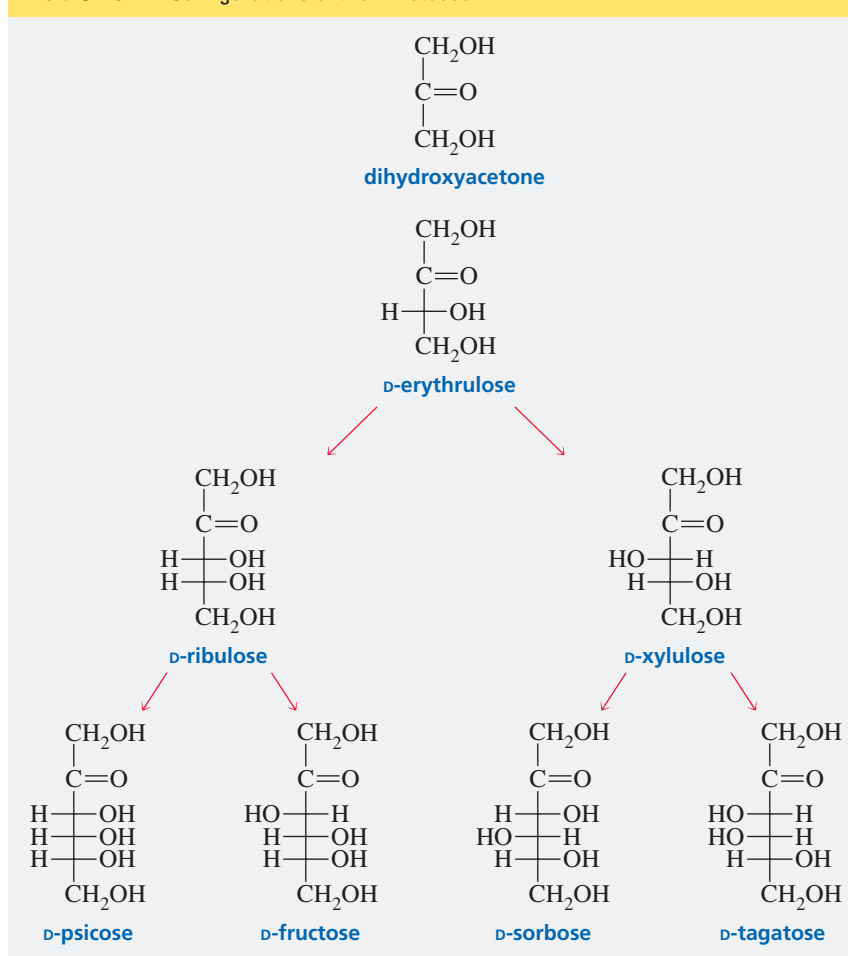
PROBLEM 5♦

What sugar is the C-3 epimer of D-fructose?

PROBLEM 6♦

How many stereoisomers are possible for

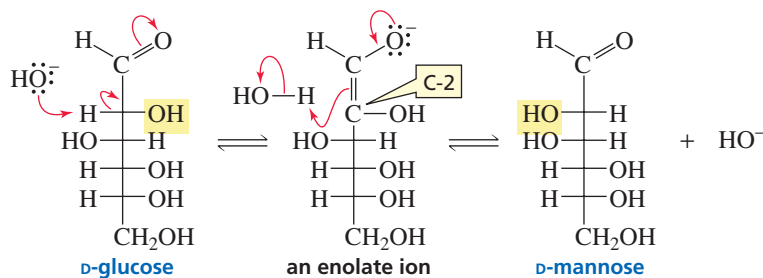
a. a ketoheptose? **b.** an aldoheptose? **c.** a ketotriose?

Table 16.2 Configurations of the D-Ketoses

16.5 THE REACTIONS OF MONOSACCHARIDES IN BASIC SOLUTIONS

In a basic solution, a monosaccharide is converted to a mixture of polyhydroxy aldehydes and polyhydroxy ketones. Let's look at what happens to D-glucose in a basic solution, beginning with its conversion to its C-2 epimer.

MECHANISM FOR THE BASE-CATALYZED EPIMERIZATION OF A MONOSACCHARIDE

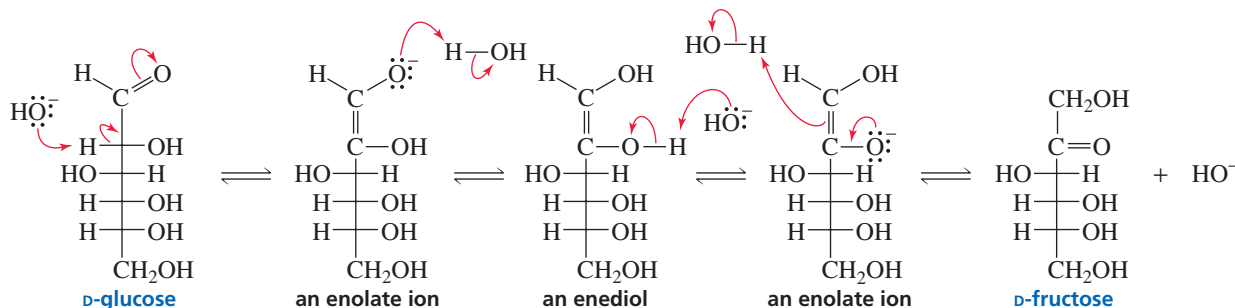
C-2

D-glucose ⇌ an enolate ion ⇌ D-mannose + HO^-

- The base removes a proton from an α-carbon, forming an enolate ion (Section 13.3). Notice that C-2 in the enolate ion is no longer an asymmetric center.
- When C-2 is reprotonated, the proton can come from the top or the bottom of the planar sp^2 carbon, forming both D-glucose and D-mannose (C-2 epimers).

Because the reaction forms a pair of epimers, it is called an epimerization. **Epimerization** changes the configuration of a carbon by removing a proton from it and then reprotonating it.

In addition to forming its C-2 epimer in a basic solution, D-glucose also undergoes an **enediol rearrangement,** which forms D-fructose and other ketohexoses.

MECHANISM FOR THE BASE-CATALYZED ENEDIOL REARRANGEMENT OF A MONOSACCHARIDE

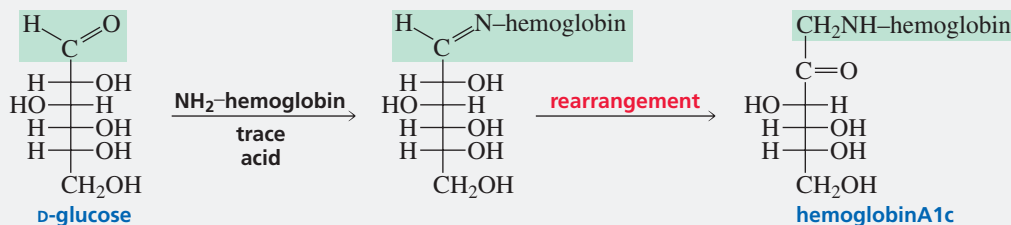
D-glucose ⇌ an enolate ion ⇌ an enediol ⇌ an enolate ion ⇌ D-fructose + HO^-

- The base removes a proton from an α-carbon, forming an enolate ion.
- Either C-2 can be protonated (as in the epimerization mechanism shown on page 558), or the oxygen of the enolate ion can be protonated to form an enediol.
- The enediol has two OH groups that can form a carbonyl group. Tautomerization of the OH at C-1 (as in base-catalyzed epimerization shown on page 558) re-forms D-glucose or forms D-mannose; tautomerization of the OH group at C-2 forms D-fructose.

Another enediol rearrangement, initiated by a base removing a proton from C-3 of D-fructose, forms an enediol that can tautomerize to give a ketose with the carbonyl group at C-2 or C-3. Thus, the carbonyl group can be moved up and down the chain.

In a basic solution, an aldose forms a C-2 epimer and one or more ketoses.

Measuring the Blood Glucose Levels in Diabetes

Glucose in the bloodstream reacts with an NH_2 group of hemoglobin to form an imine (Section 12.8) that subsequently undergoes an irreversible rearrangement to a more stable α-aminoketone known as hemoglobinA1c.

D-glucose —(NH_2–hemoglobin, trace acid)→ imine (N–hemoglobin) —rearrangement→ hemoglobinA1c (CH_2NH–hemoglobin)

Insulin is the hormone that regulates the level of glucose—and thus the amount of hemoglobinA1c—in the blood. Diabetes is a condition in which the body does not produce sufficient insulin, or in which the insulin it produces does not function properly. Because people with untreated diabetes have increased blood glucose levels, they also have a higher concentration of hemoglobinA1c than people without diabetes. Thus, measuring the hemoglobinA1c level is a way to determine whether the blood glucose level of a diabetic patient is being controlled.

Cataracts, a common complication in diabetes, are caused by the reaction of glucose with the NH_2 group of proteins in the lens of the eye. Some think the arterial rigidity common in old age may be attributable to a similar reaction of glucose with the NH_2 group of proteins.

PROBLEM 7

Show how an enediol rearrangement can move the carbonyl group of fructose from C-2 to C-3.

PROBLEM 8

Write the mechanism for the base-catalyzed conversion of D-fructose to form D-glucose and D-mannose.

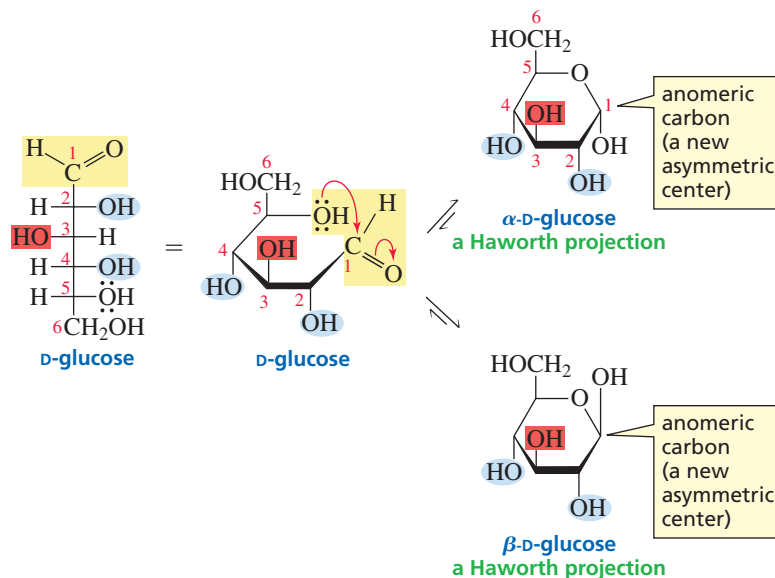
16.6 MONOSACCHARIDES FORM CYCLIC HEMIACETALS

D-Glucose exists in three different forms: the open-chain form of D-glucose that we have been discussing and two cyclic forms— α-D-glucose and β-D-glucose. We know that the two cyclic forms are different because they have different melting points and different specific rotations (Section 4.9).

How can D-glucose exist in a cyclic form? In Section 12.9, we saw that an aldehyde reacts with an alcohol to form a hemiacetal. The reaction of the alcohol group bonded to C-5 of D-glucose with the aldehyde group forms two cyclic (six-membered ring) hemiacetals.

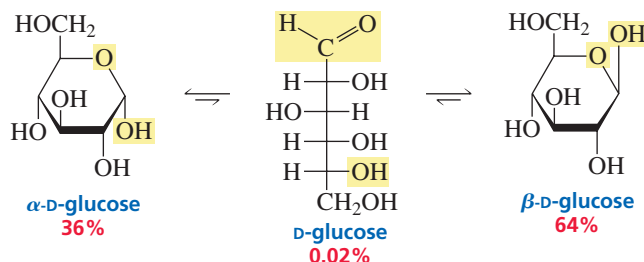
To see that the OH group on C-5 is in the proper position to add to the aldehyde group, we need to convert the Fischer projection of D-glucose to a flat ring structure. To do this, draw the primary alcohol group *up* from the back left-hand corner. Groups on the *right* in a Fischer projection are *down* in the cyclic structure, and groups on the *left* in a Fischer projection are *up* in the cyclic structure. The cyclic hemiacetals shown here are drawn as Haworth projections.

Groups on the *right* in a Fischer projection are *down* in a Haworth projection.

Groups on the *left* in a Fischer projection are *up* in a Haworth projection.

In a **Haworth projection,** the six-membered ring is represented as flat and is viewed edge on. The ring oxygen is always placed in the back right-hand corner of the ring, with C-1 on the right-hand side, and the primary alcohol group attached to C-5 is drawn *up* from the back left-hand corner.

There are two different cyclic hemiacetals because the carbonyl carbon of the open-chain aldehyde becomes a new asymmetric center in the cyclic hemiacetal. If the OH group bonded to the new asymmetric center points *down*, then the hemiacetal is α-D-glucose; if the OH group points *up*, then the hemiacetal is β-D-glucose. The mechanism for cyclic hemiacetal formation is the same as the mechanism for hemiacetal formation between individual aldehyde and alcohol molecules (Section 12.9).

α-D-Glucose and β-D-glucose are anomers. **Anomers** are two sugars that differ in configuration only at the carbon that was the carbonyl carbon in the open-chain form. This carbon is called the **anomeric carbon.** The prefixes α- and β- denote the configuration about the anomeric carbon. Anomers, like epimers, differ in configuration at only one carbon. Notice that the anomeric carbon is the only carbon in the molecule that is bonded to two oxygens.

α-D-glucose 36% ⇌ D-glucose 0.02% ⇌ β-D-glucose 64%

In an aqueous solution, the open-chain form of D-glucose is in equilibrium with the two cyclic hemiacetals. At equilibrium, there is almost twice as much β-D-glucose (64%) as α-D-glucose (36%) and very little glucose is in the open-chain form.

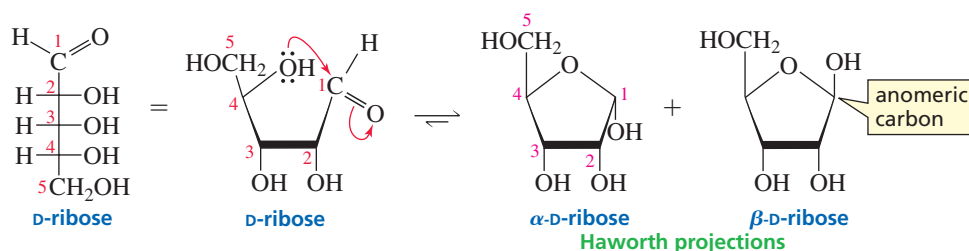
When crystals of pure α-D-glucose are dissolved in water, the specific rotation gradually changes from +112.2 to +52.7. When crystals of pure β-D-glucose are dissolved in water, the specific rotation gradually changes from +18.7 to +52.7.

This change in rotation occurs because in water, the hemiacetal opens to form the aldehyde, and both α-D-glucose and β-D-glucose are formed when the aldehyde recyclizes. Eventually, the three forms of glucose reach equilibrium concentrations. The specific rotation of the equilibrium mixture is +52.7. This is why the same specific rotation results whether the crystals originally dissolved in water are α-D-glucose or β-D-glucose or any mixture of the two. A slow change in optical rotation to an equilibrium value is called **mutarotation.**

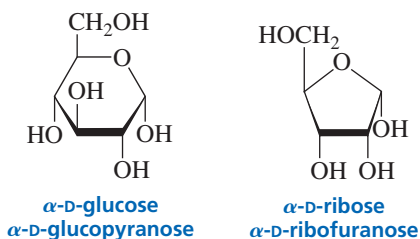
If an aldose can form a five- or a six-membered ring, it will exist predominantly as a cyclic hemiacetal in solution. D-Ribose is an example of an aldose that forms five-membered ring hemiacetals: α-D-ribose and β-D-ribose. The Haworth projection of a five-membered ring sugar is viewed edge on, with the ring oxygen pointing away from the viewer. Again, the anomeric carbon is on the right-hand side of the molecule, and the primary alcohol group is drawn *up* from the back left-hand corner. Again, notice that the anomeric carbon is the only carbon in the molecule that is bonded to two oxygens.

D-ribose = D-ribose ⇌ α-D-ribose + β-D-ribose

Haworth projections

anomeric carbon

Six-membered ring sugars are called **pyranoses,** and five-membered ring sugars are called **furanoses.** These names come from *pyran* and *furan,* the names of the cyclic ethers shown in the margin. Consequently, α-D-glucose is also called α-D-glucopyranose, and α-D-ribose is also called α-D-ribofuranose. The prefix "α" indicates the configuration about the anomeric carbon, and *pyranose* or *furanose* indicates the size of the ring.

α-D-glucose
α-D-glucopyranose

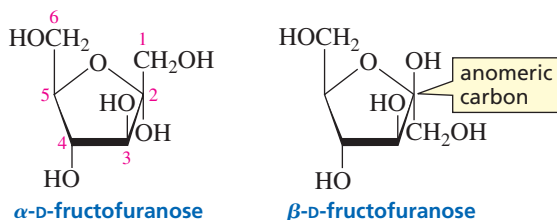
α-D-ribose
α-D-ribofuranose

pyran

furan

Ketoses also exist in solution predominantly in cyclic forms. For example, D-fructose forms a five-membered ring hemiacetal when its C-5 OH group reacts with its ketone carbonyl group. If the OH group bonded to the new asymmetric center points *down*, the compound is α-D-fructofuranose; if it points *up*, the compound is β-D-fructofuranose. Notice that the anomeric carbon is C-2 in ketoses, not C-1 as in aldoses.

α-D-fructofuranose

β-D-fructofuranose

anomeric carbon

Haworth projections are useful because they show clearly whether the OH groups on the ring are cis or trans to each other. Five-membered rings are nearly planar, so furanoses are represented fairly accurately by Haworth projections. Haworth projections, however, are structurally misleading for pyranoses because a six-membered ring is not flat—it exists preferentially in a chair conformation (Section 3.11).

Vitamin C

an English sailor circa 1829

Vitamin C (also called L-ascorbic acid) is an antioxidant because it traps radicals formed in aqueous environments, preventing harmful oxidation reactions the radicals would cause (Section 14.7). Not all the physiological functions of vitamin C are known. However, we do know that it is required for collagen fibers to form properly. Collagen is the structural protein of skin, tendons, connective tissue, and bone.

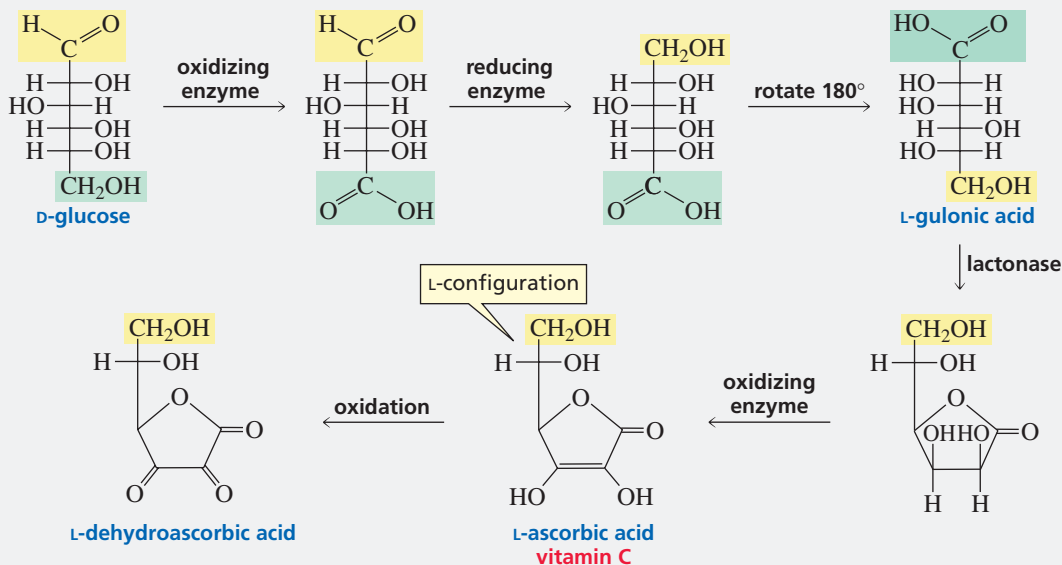
Vitamin C is abundant in citrus fruits and tomatoes. When the vitamin is not present in the diet, lesions appear on the skin, severe bleeding occurs about the gums, in the joints, and under the skin, and any wound heals slowly. The condition, known as *scurvy*, was the first disease to be treated by adjusting the diet. British sailors who shipped out to sea after the late 1700s were required to eat limes to prevent scurvy (which is how they came to be called “limeys”). Not until 200 years later did it become known that the substance preventing scurvy was vitamin C. *Scorbutus* is Latin for “scurvy”; *ascorbic*, therefore, means “no scurvy.”

Vitamin C is synthesized from D-glucose in plants and in the livers of most vertebrates. Primates and guinea pigs do not have the enzymes necessary for the biosynthesis of vitamin C, so they must obtain the vitamin from their diets.

STEPS IN THE SYNTHESIS OF L-ASCORBIC ACID

D-glucose → (oxidizing enzyme) → → (reducing enzyme) → → (rotate 180°) → L-gulonic acid

L-gulonic acid → (lactonase) → → (oxidizing enzyme) → L-ascorbic acid (vitamin C) → (oxidation) → L-dehydroascorbic acid

L-configuration

In the first step of the biosynthesis of vitamin C, the primary alcohol group of D-glucose is oxidized to a carboxylic acid. Next, the aldehyde group is reduced to a primary alcohol, forming L-gulonic acid. L-Gulonic acid is converted into a cyclic ester by the enzyme lactonase. The cyclic ester is oxidized to L-ascorbic acid. The L-designation of ascorbic acid refers to the configuration at C-5, which was C-2 in D-glucose and C-5 in L-gulonic acid.

L-Ascorbic acid is readily oxidized to L-dehydroascorbic acid, which is also physiologically active. If the ring of the cyclic ester is opened by hydrolysis, all vitamin C activity is lost. Therefore, not much intact vitamin C survives in food that has been thoroughly cooked. And if food is cooked in water and then drained, the water-soluble vitamin is thrown out with the water!

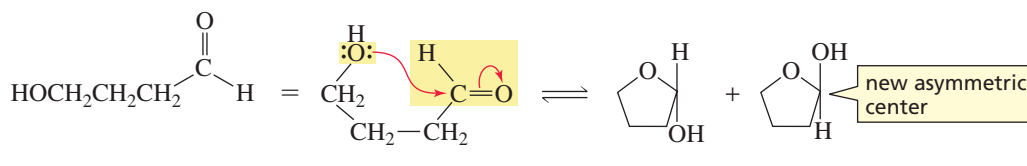
PROBLEM 9 Solved

4-Hydroxy- and 5-hydroxyaldehydes exist primarily as cyclic hemiacetals. Draw the structure of the cyclic hemiacetal formed by each of the following:

a. 4-hydroxybutanal **b.** 4-hydroxypentanal **c.** 5-hydroxypentanal **d.** 4-hydroxyheptanal

Solution to 9a Draw the reactant with its alcohol and carbonyl groups on the same side of the molecule, then look to see what size ring will form. Two cyclic products are obtained because the carbonyl carbon of the reactant has been converted into a new asymmetric center in the product.

$HOCH_2CH_2CH_2CHO$ = (reactant drawn with :O:H and C=O on same side) ⇌ (cyclic hemiacetal, OH down) + (cyclic hemiacetal, OH up)

new asymmetric center

PROBLEM 10

Draw each of the following sugars using Haworth projections:

a. β-D-galactopyranose **b.** α-D-tagatopyranose **c.** α-D-glucopyranose

16.7 GLUCOSE IS THE MOST STABLE ALDOHEXOSE

Drawing D-glucose in its chair conformation shows why it is the most common aldohexose in nature. To convert the Haworth projection of D-glucose into a chair conformer, start by drawing the chair so that the backrest is on the left and the footrest is on the right. Then place the ring oxygen at the back right-hand corner and the primary alcohol group in the equatorial position. The primary alcohol group is the largest of all the substituents, and we know that large substituents are more stable in the equatorial position because there is less steric strain in that position (Section 3.12).

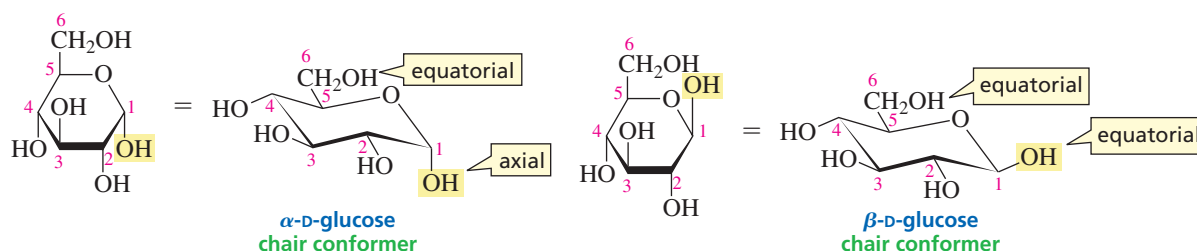
equatorial

axial

equatorial

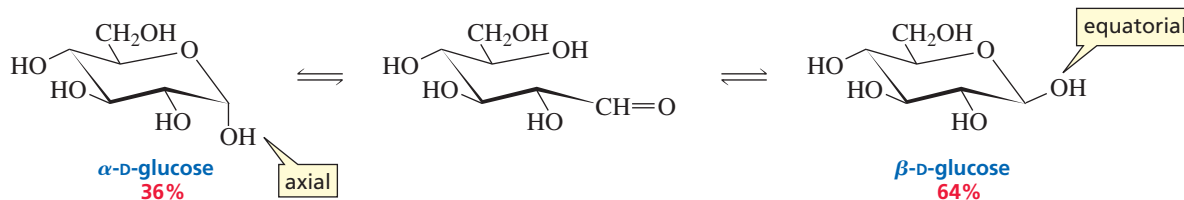
equatorial

α-D-glucose chair conformer

β-D-glucose chair conformer

Because the OH group bonded to C-4 is trans to the primary alcohol group (this is easily seen in the Haworth projection), the C-4 OH group is also in the equatorial position. (Recall from Section 3.13 that 1,2-diequatorial substituents are trans to one another.) The C-3 OH group is trans to the C-4 OH group, so the C-3 OH group is also in the equatorial position. As you move around the ring, you will find that all the OH substituents in β-D-glucose are in equatorial positions. The axial positions are all occupied by hydrogens, which require little space and, therefore, experience little steric strain. No other aldohexose exists in such a strain-free conformation. This means that β-D-glucose is the most stable of all the aldohexoses, so we should not be surprised that it is the most prevalent aldohexose in nature.

All the OH groups in β-D-glucose are in equatorial positions.

The OH group bonded to the anomeric carbon is in the equatorial position in β-D-glucose, whereas it is in the axial position in α-D-glucose. Therefore, β-D-glucose is more stable than α-D-glucose, so β-D-glucose predominates at equilibrium in an aqueous solution.

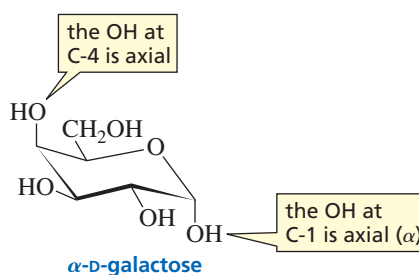
α-D-glucose 36% (OH axial) ⇌ open-chain (CH=O) ⇌ β-D-glucose 64% (OH equatorial)

The α-position is down in a Haworth projection and axial in a chair conformation.

The β-position is up in a Haworth projection and equatorial in a chair conformation.

If you remember that all the OH groups in β-D-glucose are in equatorial positions, you will find it easy to draw the chair conformer of any other pyranose. For example, if you want to draw α-D-galactose, you would put all the OH groups in equatorial positions except the OH group at C-4 (because galactose is the C-4 epimer of glucose) and the OH group at C-1 (because you want the α-anomer), which both go in axial positions.

the OH at C-4 is axial

the OH at C-1 is axial (α)

α-D-galactose

PROBLEM 11 ♦ Solved

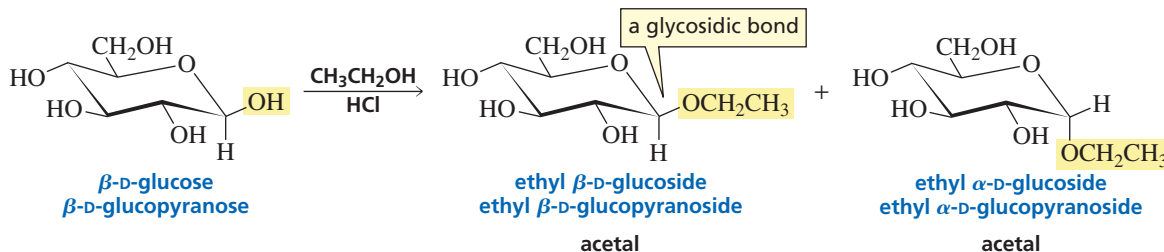
Which OH groups are in the axial position in

a. β-D-mannopyranose? **b.** β-D-idopyranose? **c.** α-D-allopyranose?

Solution to 11a All the OH groups in β-D-glucose are in equatorial positions. Because β-D-mannose is the C-2 epimer of β-D-glucose, only the C-2 OH group of β-D-mannose is in the axial position.

16.8 FORMATION OF GLYCOSIDES

In the same way that a hemiacetal reacts with an alcohol to form an acetal (Section 12.9), the cyclic hemiacetal formed by a monosaccharide can react with an alcohol to form two acetals.

β-D-glucose / β-D-glucopyranose $\xrightarrow[HCl]{CH_3CH_2OH}$ ethyl β-D-glucoside / ethyl β-D-glucopyranoside (acetal; OCH_2CH_3 — a glycosidic bond) + ethyl α-D-glucoside / ethyl α-D-glucopyranoside (acetal)

The acetal of a sugar is called a **glycoside,** and the bond between the anomeric carbon and the alkoxy oxygen is called a **glycosidic bond.** Glycosides are named by replacing the “e” ending of the sugar’s name with “ide.” Thus, a glycoside of glucose is a glucoside, a glycoside of galactose is a galactoside, and so on. If the pyranose or furanose name is used, the acetal is called a **pyranoside** or a **furanoside.**

Notice that the reaction of a single anomer of the cyclic hemiacetal with an alcohol leads to the formation of both the α- and β-glycosides. The mechanism of the reaction shows why both glycosides are formed.

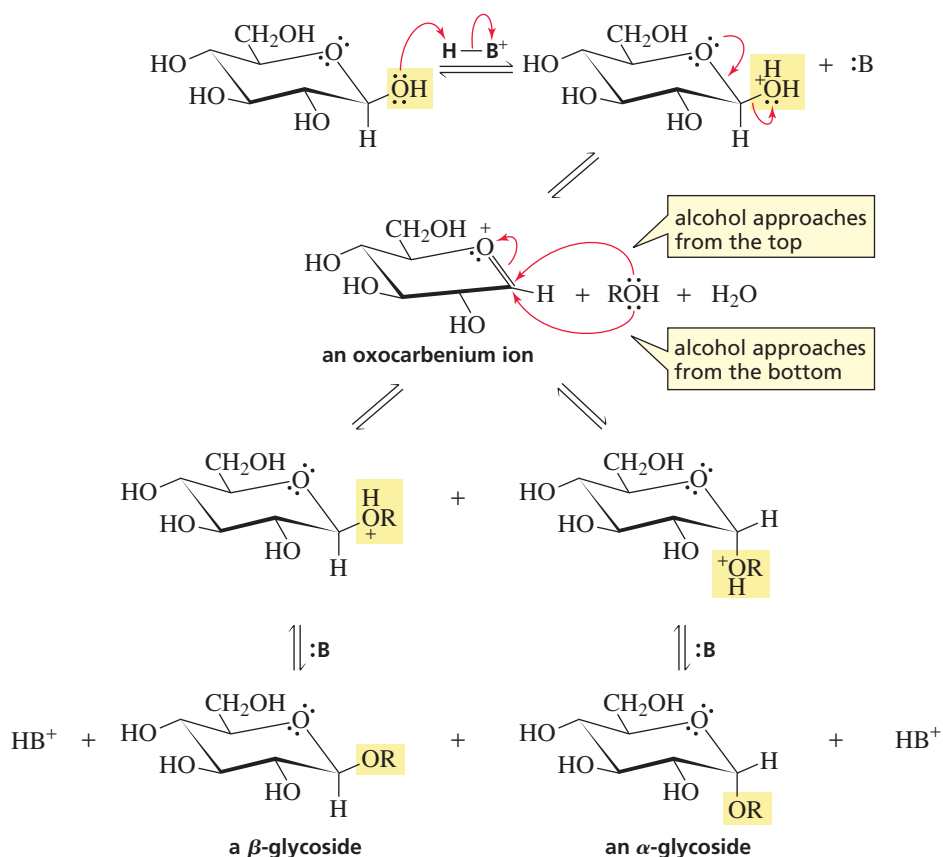
MECHANISM FOR GLYCOSIDE FORMATION

alcohol approaches from the top

alcohol approaches from the bottom

an oxocarbenium ion

a β-glycoside

an α-glycoside

- The acid protonates the OH group bonded to the anomeric carbon.
- A lone pair on the ring oxygen helps eliminate a molecule of water. The anomeric carbon in the resulting oxocarbenium ion is sp^2 hybridized, so that part of the molecule is planar. (An **oxocarbenium** ion has a positive charge that is shared by a carbon and an oxygen.)
- When the alcohol approaches from the top of the plane, the β-glycoside is formed; when the alcohol approaches from the bottom of the plane, the α-glycoside is formed.

Notice that the mechanism is the same as that shown for acetal formation in Section 12.9.

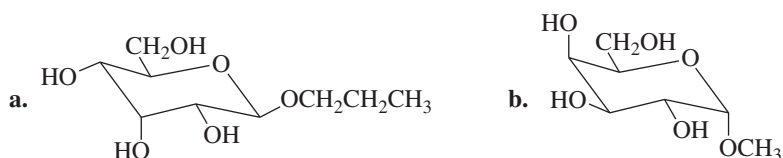
PROBLEM 12

Draw the products formed when β-D-galactose reacts with ethanol and HCl.

PROBLEM 13 ♦ Solved

Name the following compounds:

a. $OCH_2CH_2CH_3$

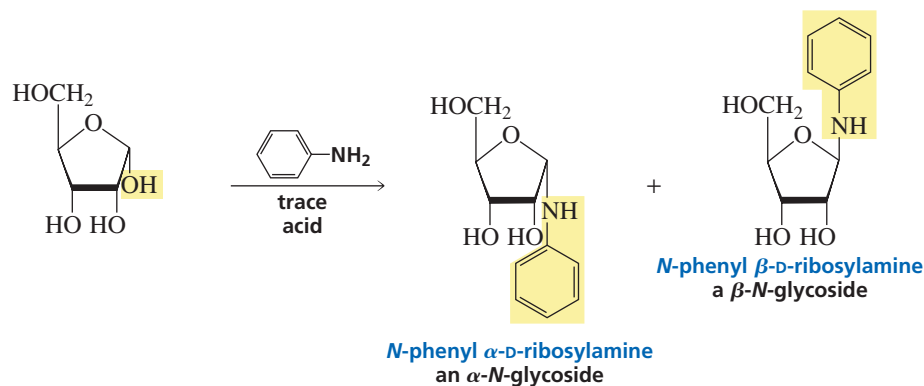
b. OCH_3

Solution to 13a The only OH group in an axial position in part **a** is the one at C-3. Therefore, this sugar is the C-3 epimer of D-glucose, which is D-allose. The substituent at the anomeric carbon is in the β-position. Thus, the sugar's name is propyl β-D-alloside or propyl β-D-allopyranoside.

The reaction of a monosaccharide with an amine is similar to the reaction of a monosaccharide with an alcohol. The product of the reaction is an *N*-glycoside. An ***N*-glycoside** has a nitrogen in place of the oxygen at the glycosidic linkage. The subunits of DNA and RNA are β-*N*-glycosides (Section 21.1).

HOCH₂ ... OH ... HO HO — NH₂ (aniline), trace acid →

N-phenyl α-D-ribosylamine
an α-N-glycoside

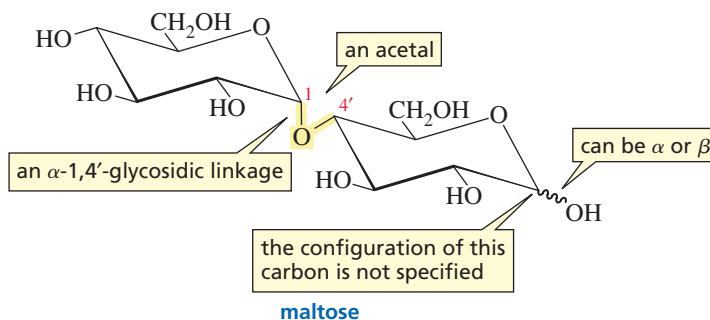
+

N-phenyl β-D-ribosylamine
a β-N-glycoside

PROBLEM 14 ♦

Why is only a trace amount of acid used in the formation of an *N*-glycoside?

16.9 DISACCHARIDES

If the hemiacetal group of a monosaccharide forms an acetal by reacting with an alcohol group of another monosaccharide, the glycoside that is formed is a disaccharide. **Disaccharides** are compounds that consist of two monosaccharide subunits hooked together by a glycosidic linkage.

For example, maltose, a disaccharide obtained from the hydrolysis of starch, contains two D-glucose subunits connected by a glycosidic linkage. This particular linkage is called an **α-1,4′-glycosidic linkage** because the linkage is between C-1 of one sugar subunit and C-4 of the other, and the oxygen bonded to the anomeric carbon in the glycosidic linkage is in the α-position. The prime superscript indicates that C-4 is not in the same ring as C-1.

Remember that the α-position is axial and the β-position is equatorial when a sugar is shown in a chair conformation.

an acetal

an α-1,4′-glycosidic linkage

can be α or β

the configuration of this carbon is not specified

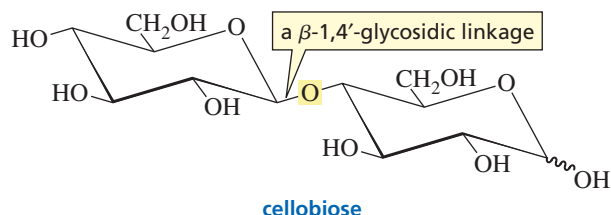
maltose

Notice that the structure of maltose does not specify the configuration of the anomeric carbon that is not an acetal (the anomeric carbon of the subunit on the right marked with a wavy line) because maltose can exist in both the α and β forms. In α-maltose, the OH group bonded to this anomeric carbon is in the axial position. In β-maltose, the OH group is in the equatorial position.

Cellobiose, a disaccharide obtained from the hydrolysis of cellulose, also contains two D-glucose subunits. Cellobiose is different from maltose, however, because the two

glucose subunits are hooked together by a **β-1,4′-glycosidic linkage.** Thus, the only difference in the structures of maltose and cellobiose is the configuration of the glycosidic linkage. Like maltose, cellobiose exists in both α and β forms because the OH group bonded to the anomeric carbon not involved in acetal formation can be in either the axial position (in α-cellobiose) or the equatorial position (in β-cellobiose).

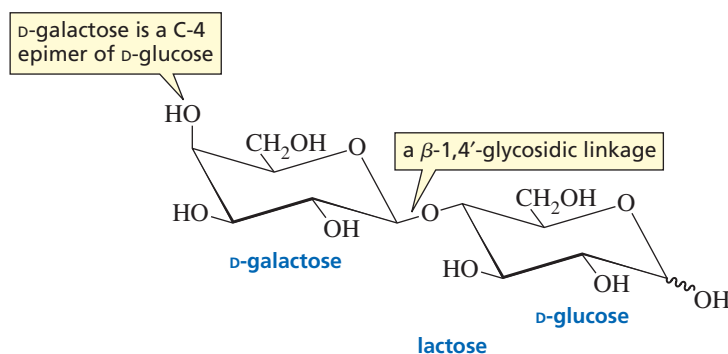
a β-1,4′-glycosidic linkage

cellobiose

Lactose is a disaccharide found in milk. The subunits of lactose are D-galactose and D-glucose. The D-galactose subunit is an acetal, and the D-glucose subunit is a hemiacetal. The subunits are joined by a β-1,4′-glycosidic linkage.

D-galactose is a C-4 epimer of D-glucose

a β-1,4′-glycosidic linkage

D-galactose

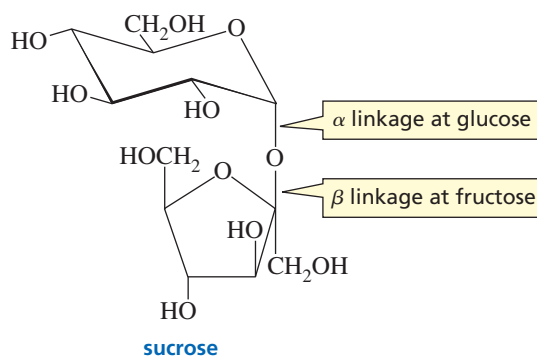
D-glucose

lactose

Lactose Intolerance

Lactase is an enzyme that specifically breaks the β-1,4′-glycosidic linkage of lactose. Cats and dogs lose their intestinal lactase when they become adults; they are then no longer able to digest lactose. Consequently, when they are fed milk or milk products, the undegraded lactose causes digestive problems such as bloating, abdominal pain, and diarrhea. These problems occur because only monosaccharides can pass into the bloodstream, so lactose, a disaccharide, has to pass undigested into the large intestine.

When humans have stomach flu or other intestinal disturbances, they can temporarily lose their lactase, thereby becoming lactose intolerant. About 75% of adults lose their lactase permanently as they mature—explaining why “lactose-free” products are so common. Those intolerant to lactose can take lactase in pill form before eating products that contain lactose.

Lactose intolerance is most common in people whose ancestors came from non-dairy-producing countries. For example, only 3% of Danes are lactose intolerant, compared with 90% of all Chinese and Japanese and 97% of Thais. This is why you are not likely to find dairy items on menus in Chinese restaurants.

The most common disaccharide, sucrose, is the substance we know as table sugar. Obtained from sugar beets and sugar cane, sucrose consists of a D-glucose subunit and a D-fructose subunit linked by a glycosidic bond between C-1 of glucose (in the α-position) and C-2 of fructose (in the β-position).

sucrose

a mixture of sucrose, glucose, and fructose

Sucrose has a specific rotation of +66.5. When it is hydrolyzed, the resulting 1 : 1 mixture of glucose and fructose has a specific rotation of −22.0. Because the sign of the rotation changes when sucrose is hydrolyzed, a 1 : 1 mixture of glucose and fructose is called *invert sugar*. The enzyme that catalyzes the hydrolysis of sucrose is called *invertase*. Honeybees have invertase, so the honey they produce is a mixture of sucrose, glucose, and fructose. Because fructose is sweeter than sucrose, invert sugar is also sweeter than sucrose.

Some "lite" foods contain fructose instead of sucrose, which means that they achieve the same level of sweetness with a lower sugar (lower calorie) content.

PROBLEM 15 ♦

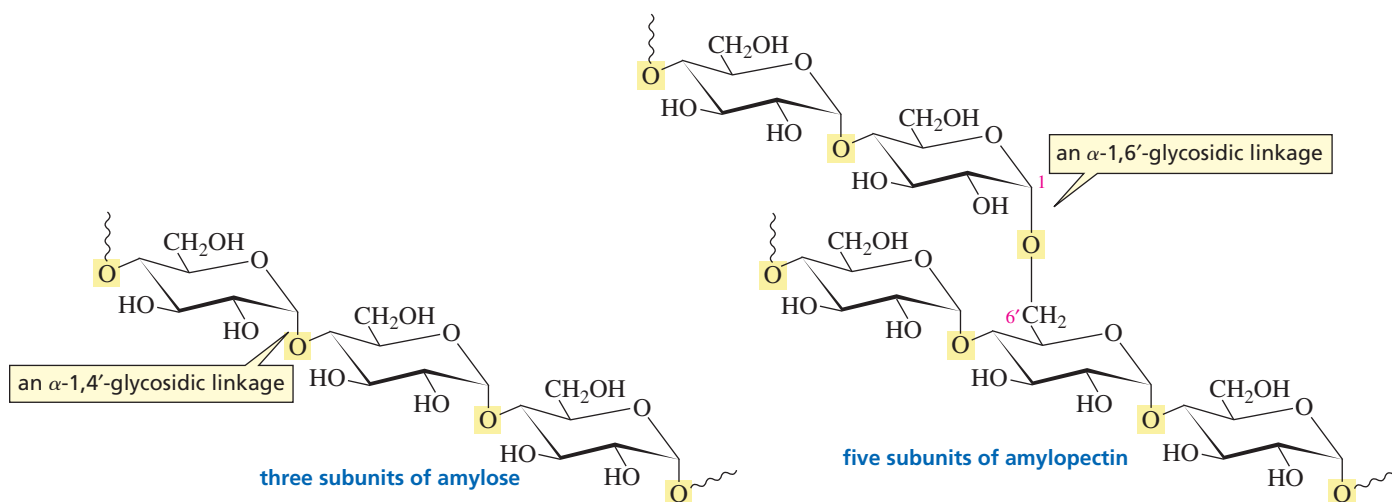
What is the specific rotation of an equilibrium mixture of fructose? (*Hint:* The specific rotation of an equilibrium mixture of glucose is +52.7.)

16.10 POLYSACCHARIDES

Polysaccharides contain as few as 10 or as many as several thousand monosaccharide units joined together by glycosidic linkages. The most common polysaccharides are starch and cellulose.

Starch is the major component of flour, potatoes, rice, beans, corn, and peas. It is a mixture of two different polysaccharides: amylose (~20%) and amylopectin (~80%). Amylose is composed of unbranched chains of D-glucose units joined by α-1,4′-glycosidic linkages.

three subunits of amylose

five subunits of amylopectin

Amylopectin is a branched polysaccharide. Like amylose, it is composed of chains of D-glucose units joined by α-1,4′-glycosidic linkages. Unlike amylose, however, amylopectin also contains **α-1,6′-glycosidic linkages.** These linkages create branches in the polysaccharide (Figure 16.1). Amylopectin can contain up to 10^6 glucose units, making it one of the largest molecules found in nature.

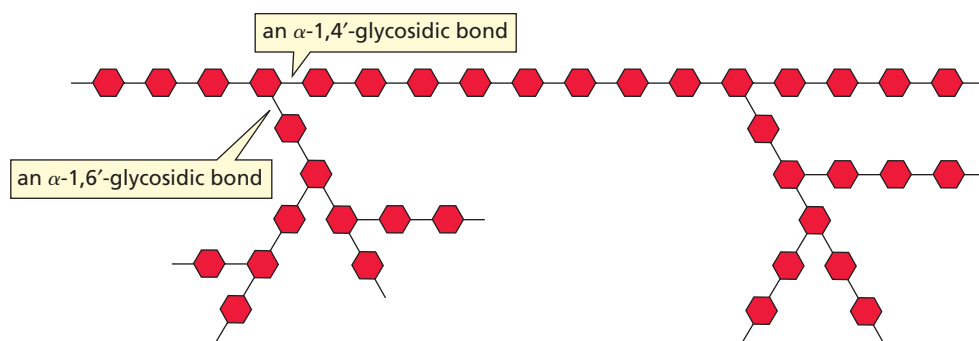



Figure 16.1
Branching in amylopectin. The hexagons represent glucose units. They are joined by α-1,4′- and α-1,6′-glyclosidic bonds.

Cells oxidize D-glucose in the first of a series of processes that provide them with energy (Section 19.5). When animals have more D-glucose than they need for energy, they convert the excess D-glucose into a polymer called glycogen. Glycogen has a structure similar to that of amylopectin, but glycogen has more branches (Figure 16.2). The high degree of branching in glycogen has important physiological consequences. When an animal needs energy, many individual glucose units can be simultaneously removed from the ends of many branches. Plants convert excess D-glucose into starch.

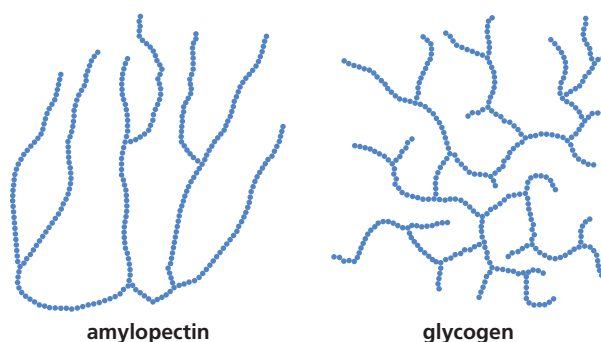



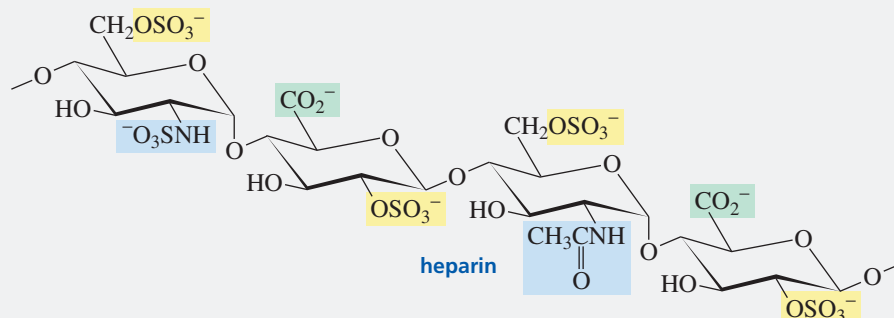
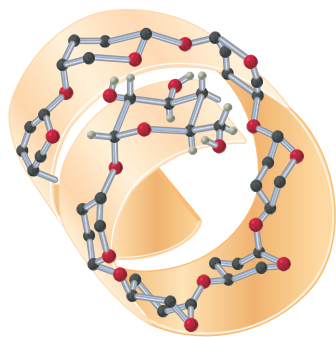
Figure 16.2
A comparison of the branching in amylopectin and glycogen.

Why the Dentist Is Right

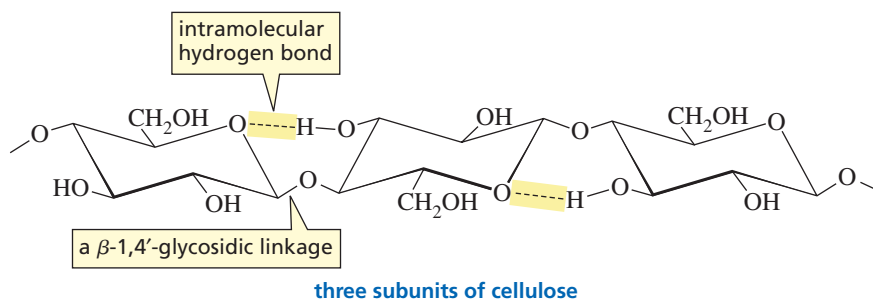
Bacteria found in the mouth have an enzyme that converts sucrose into a polysaccharide called dextran. Dextran is made up of glucose units joined mainly through α-1,3′- and α-1,6′-glycosidic linkages. About 10% of dental plaque is composed of dextran, and bacteria hidden in the plaque attack tooth enamel. This is the chemical basis for your dentist's warning not to eat candy. This is also why sorbitol and mannitol are the saccharides added to "sugarless" gum—they cannot be converted to dextran.

Heparin—A Natural Anticoagulant

Heparin is a polysaccharide found principally in cells that line arterial walls. Some of its alcohol and amino groups are sulfonated, some of its primary alcohol groups are oxidized, and some of its amino groups are acetylated. Heparin is released to prevent excessive blood clot formation when an injury occurs. Heparin is widely used clinically—particularly after surgery—to prevent blood from clotting.

heparin

▲ **Figure 16.3**
The α-1,4′-glycosidic linkages in amylose cause it to form a left-handed helix. Many of its OH groups form hydrogen bonds with water molecules.

Cellulose is the major structural component of plants. Cotton, for example, is composed of about 90% cellulose, and wood is about 50% cellulose. Like amylose, cellulose is composed of unbranched chains of D-glucose units. Unlike amylose, however, the glucose units in cellulose are joined by β-1,4′-glycosidic linkages rather than by α-1,4′-glycosidic linkages.

three subunits of cellulose

The different glycosidic linkages in starch and cellulose give these compounds very different physical properties. The α-linkages in starch cause amylose to form a helix that promotes hydrogen bonding of its OH groups to water molecules (Figure 16.3). As a result, starch is soluble in water.

strands of cellulose in a plant cell wall

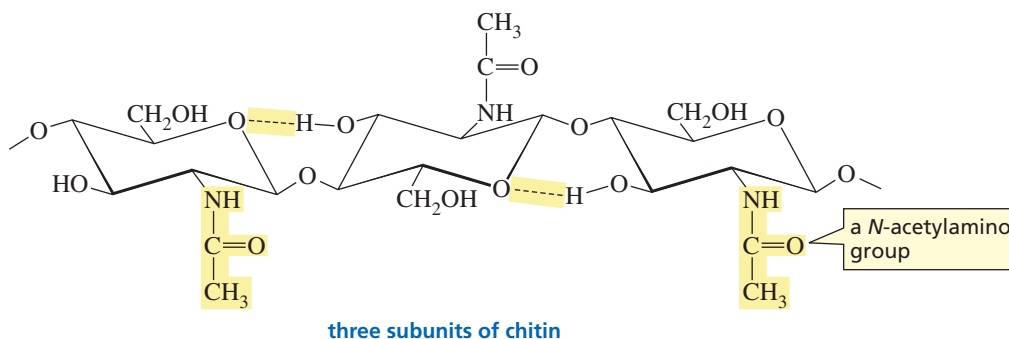
On the other hand, the β-linkages in cellulose promote the formation of intramolecular hydrogen bonds. Consequently, these molecules form linear arrays, held together by hydrogen bonds between adjacent chains. These large aggregates cause cellulose to be insoluble in water. The strength of these bundles of polymer chains makes cellulose an effective structural material. Processed cellulose is also used for the production of paper and cellophane.

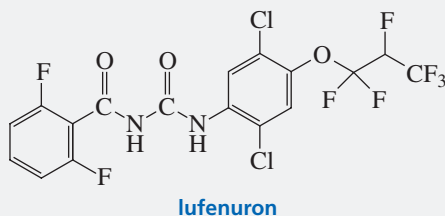
All mammals have the enzyme (α-glucosidase) that hydrolyzes the α-1,4′-glycosidic linkages that join glucose units in amylose, amylopectin, and glycogen, but they do *not* have the enzyme (β-glucosidase) that hydrolyzes β-1,4′-glycosidic linkages. As a result, mammals *cannot* obtain the glucose they need by eating cellulose. However, bacteria that possess β-glucosidase inhabit the digestive tracts of grazing animals, so cows can eat grass and horses can eat hay to meet their nutritional requirements for glucose. Termites also harbor bacteria that break down the cellulose in the wood they eat.

Chitin (KY-tin) is a polysaccharide that is structurally similar to cellulose. It is the major structural component of the shells of crustaceans (such as lobsters, crabs, and shrimp) and the exoskeletons of insects and other arthropods, and it is also the structural material of fungi. Like cellulose, chitin has β-1,4′-glycosidic linkages. Unlike cellulose, chitin has an *N*-acetylamino group instead of an OH group at the C-2 position. The β-1,4′-glycosidic linkages give chitin its structural rigidity.

The shell of this bright orange crab from Australia is composed largely of chitin.

a *N*-acetylamino group

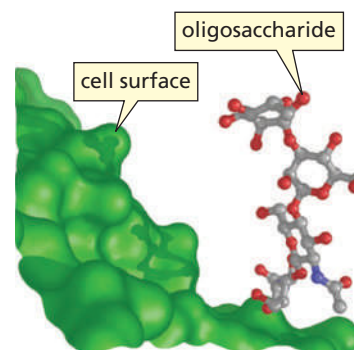
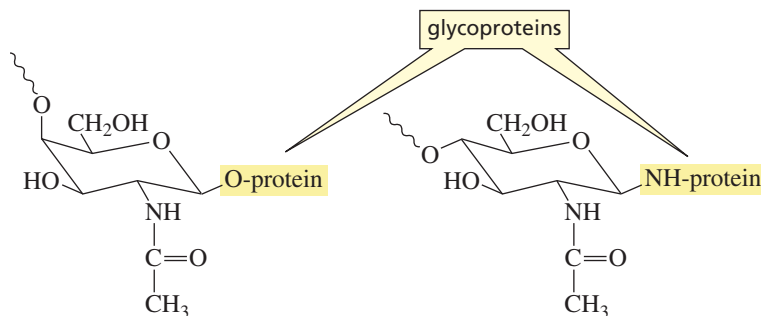
three subunits of chitin

Controlling Fleas

Several different drugs have been developed to help pet owners control fleas. One of these drugs is lufenuron, the active ingredient in Program. Lufenuron interferes with the flea's production of chitin. The consequences are fatal for the flea because its exoskeleton is composed primarily of chitin.

PROBLEM 16 ♦

What is the main structural difference between

a. amylose and cellulose?
b. amylose and amylopectin?
c. amylopectin and glycogen?
d. cellulose and chitin?

16.11 CARBOHYDRATES ON CELL SURFACES

Many cells have short oligosaccharide chains on their surface that enable the cells to recognize and interact with other cells and with invading viruses and bacteria. These oligosaccharides are linked to the surface of the cell by the reaction of an OH or an NH_2 group of a cell-membrane protein with the anomeric carbon of a cyclic sugar. Proteins attached to oligosaccharides are called **glycoproteins.**

Carbohydrates on the surfaces of cells provide a way for cells to recognize one another, serving as points of attachment for other cells, viruses, and toxins. Therefore, surface carbohydrates have been found to play a role in activities as diverse as infection, prevention of infection, fertilization, inflammatory diseases such as rheumatoid arthritis and septic shock, and blood clotting. Carbohydrate interactions also are involved in the regulation of cell growth, so changes in membrane glycoproteins are thought to be correlated with malignant transformations.

Differences in blood type (A, B, or O) are actually differences in the sugars bound to the surfaces of red blood cells. Each type of blood is associated with a different carbohydrate structure (Figure 16.4). Type AB blood is a mixture of type A blood and type B blood.

Antibodies are proteins that are synthesized by the body in response to foreign substances called *antigens*. Interaction with the antibody causes the antigen to either precipitate or be flagged for destruction by immune system cells. This is why blood

cannot be transferred from one person to another unless the blood types of the donor and acceptor are compatible. Otherwise the donated blood will be considered a foreign substance and will provoke an immune response.

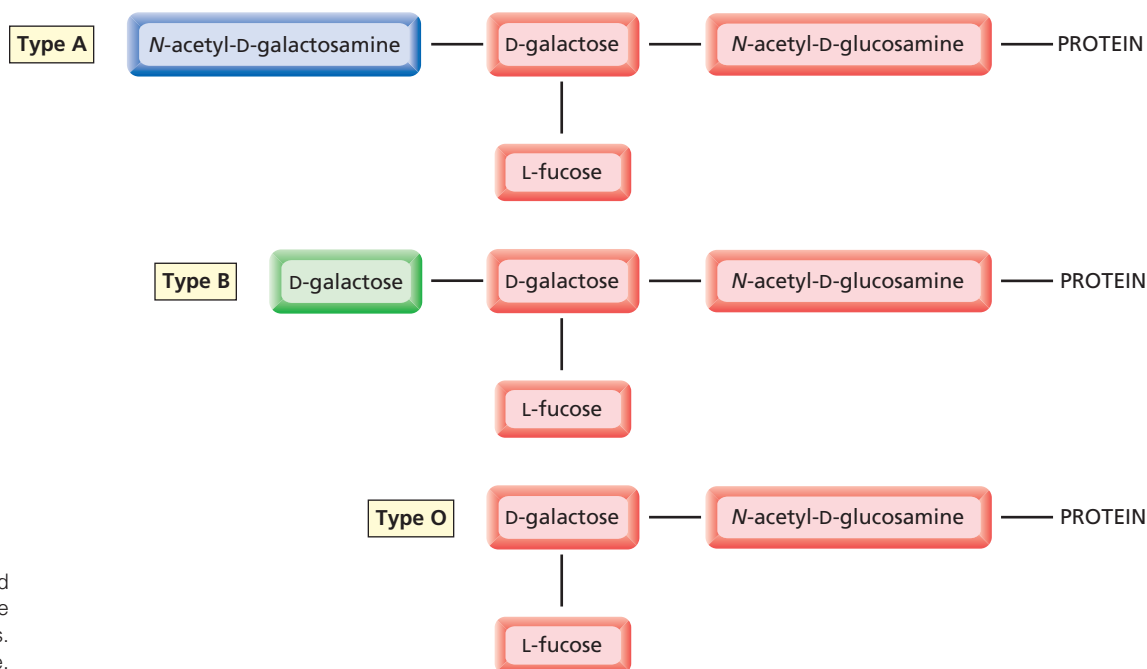



Figure 16.4
Blood type is determined by the sugars on the surfaces of red blood cells. Fucose is 6-deoxygalactose.

Looking at Figure 16.4, we can see why the immune system of people with type A blood recognizes type B blood as foreign and vice versa. The immune system of people with type A, B, or AB blood does not recognize type O blood as foreign because the carbohydrate in type O blood is also a component of types A, B, and AB blood. Thus, anyone can accept type O blood, so people with that blood type are called universal donors. People with type AB blood can accept types AB, A, B, and O blood, so they are referred to as universal acceptors.

PROBLEM 17 ♦

Refer to Figure 16.4 to answer the following questions:

a. People with type O blood can donate blood to anyone, but they cannot receive blood from everyone. From whom can they not receive blood?

b. People with type AB blood can receive blood from anyone, but they cannot give blood to everyone. To whom can they not give blood?

16.12 ARTIFICIAL SWEETENERS

Table 16.3 Relative Sweetness

Glucose	1.00
Sucrose	1.45
Fructose	1.65
Aspartame	200
Acesulfame potassium	200
Saccharine	300
Splenda	600

For a molecule to taste sweet, it must bind to a receptor on a taste bud cell on the tongue. The binding of this molecule causes a nerve impulse to pass from the taste bud to the brain, where the molecule is interpreted as being sweet. Sugars differ in their degree of "sweetness" (Table 16.3).

Developers of artificial sweeteners must evaluate potential products in terms of several factors—such as toxicity, stability, and cost—in addition to taste. Saccharin (Sweet'N Low), the first synthetic sweetener, was discovered accidentally by Ira Remsen in 1879. One evening he noticed that the dinner rolls initially tasted sweet and then bitter. Because his wife did not notice that the rolls had an unusual taste, Remsen tasted his fingers and found they had the same odd taste. The next day he tasted the chemicals he had been

working with the day before and found one that had an extremely sweet taste. (As strange as it may seem today, at one time it was common for chemists to taste compounds in order to characterize them.) He called this compound saccharin. Notice that, in spite of its name, saccharin is not a saccharide.

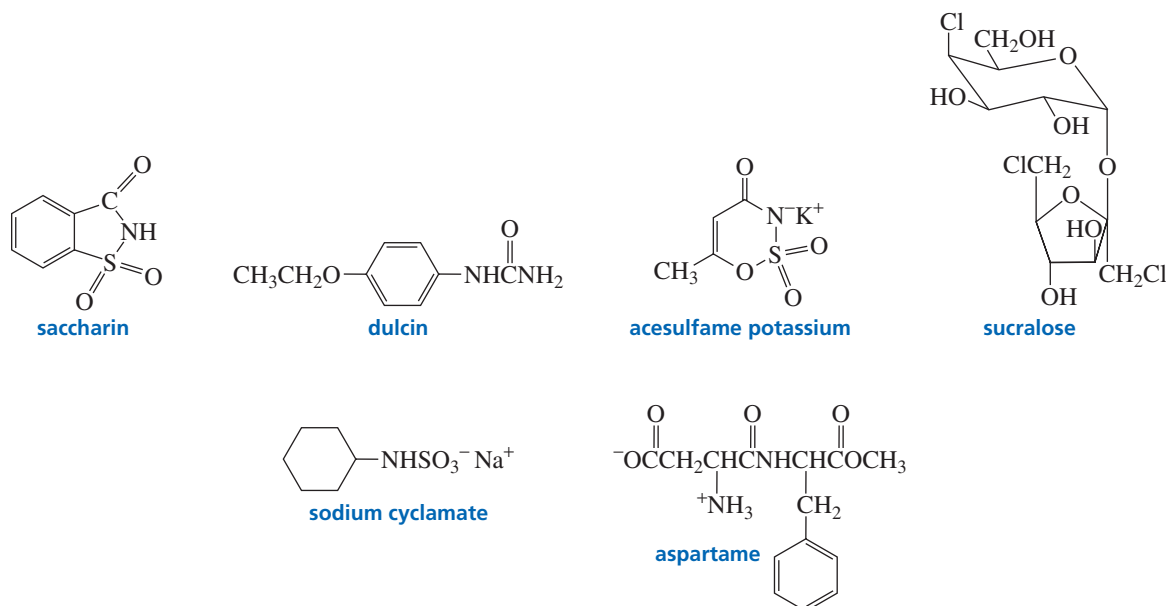
saccharin

dulcin

acesulfame potassium

sucralose

sodium cyclamate

aspartame

Because it has little caloric value, saccharin became an important substitute for sucrose when it became commercially available in 1885. The chief nutritional problem in the West was—and still is—the overconsumption of sugar and its consequences: obesity, heart disease, and dental decay. Saccharin is also a boon to people with diabetes, who must limit their consumption of sucrose and glucose. Although the toxicity of saccharin had not been studied carefully when it was first marketed (our current concern with toxicity is a fairly recent development), extensive studies since then have shown saccharin to be harmless. In 1912, saccharin was temporarily banned in the United States, not because of any concern about its toxicity, but because of a concern that people would miss out on the nutritional benefits of sugar.

Dulcin was the second synthetic sweetener to be discovered (in 1884). Even though it did not have the bitter, metallic aftertaste associated with saccharin, it never achieved much popularity. Dulcin was taken off the market in 1951 in response to concerns about its toxicity.

Sodium cyclamate became a widely used nonnutritive sweetener in the 1950s, but was banned in the United States some 20 years later in response to two studies that appeared to show that large amounts of sodium cyclamate cause liver cancer in mice.

Aspartame (NutraSweet, Equal) was approved by the U.S. Food and Drug Administration (FDA) in 1981. Because aspartame contains a phenylalanine subunit, it should not be used by people with the genetic disease known as phenylketonuria (PKU) (see page 623).

Acesulfame potassium (Sweet and Safe, Sunette, Sweet One) was approved in 1988. It has less aftertaste than saccharine and is more stable than aspartame at high temperatures.

Sucralose (Splenda) is the most recently approved (1991) synthetic sweetener. It maintains its sweetness in foods stored for long periods and at temperatures used in baking. Sucralose is made from sucrose by selectively replacing three of sucrose's OH groups with chlorines. During chlorination, the 4-position of the glucose ring becomes inverted, so sucralose is a galactopyranoside, not a glucopyranoside. Sucralose is the only artificial sweetener that has a carbohydrate-like structure. However, because of the chlorine atoms, the body does not recognize it as a carbohydrate, so it is eliminated from the body instead of being metabolized.

The fact that these synthetic sweeteners have such different structures shows that the sensation of sweetness is not induced by a single molecular shape.

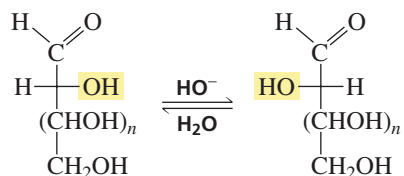
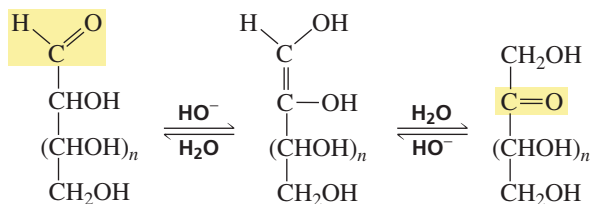
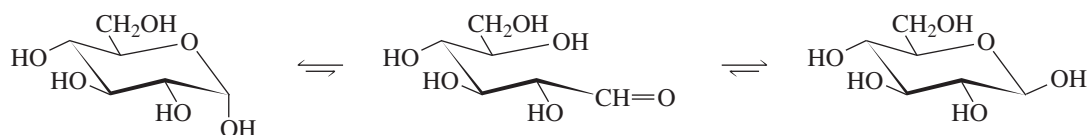
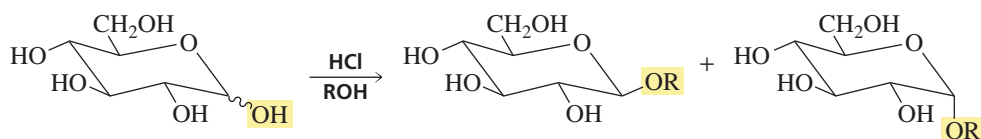
Acceptable Daily Intake

The FDA has established an acceptable daily intake (ADI) value for many of the food ingredients it clears for use. The ADI is the amount of the substance a person can consume safely, each day of his or her life. For example, the ADI for acesulfame potassium is 15 mg/kg/day. This means that each day a 132-lb person can consume the amount of acesulfame potassium that would be found in two gallons of an artificially sweetened beverage. The ADI for sucralose is 5 mg/kg/day.

SOME IMPORTANT THINGS TO REMEMBER

- **Bioorganic compounds**—organic compounds found in living systems—obey the same chemical principles that smaller organic molecules do.
- Much of the structure of bioorganic compounds exists for the purpose of **molecular recognition.**
- **Carbohydrates** are polyhydroxy aldehydes (**aldoses**) or polyhydroxy ketones (**ketoses**), or compounds formed by linking up aldoses and ketoses.
- The notations D and L describe the configuration of the bottommost asymmetric center of a **monosaccharide** in a Fischer projection. The configurations of the other asymmetric centers are inherent in the name. Most naturally occurring sugars are D-sugars.
- Naturally occurring ketoses have the ketone group in the 2-position.
- **Epimers** differ in configuration at only one asymmetric center: D-mannose is the C-2 epimer of D-glucose and D-galactose is the C-4 epimer of D-glucose.
- In a basic solution, a monosaccharide is converted to a mixture of polyhydroxy aldehydes and polyhydroxy ketones.
- The aldehyde or keto group of a **monosaccharide** reacts with one of its OH groups to form cyclic hemiacetals: glucose forms α-D-glucose and β-D-glucose. More β-D-glucose is present than α-D-glucose in an aqueous solution at equilibrium.
- α-D-Glucose and β-D-glucose are **anomers**—they differ in configuration only at the **anomeric carbon,** which is the carbon that was the carbonyl carbon in the open-chain form.
- A slow change in optical rotation to an equilibrium value is called **mutarotation.**
- The α-position is axial when a sugar is shown in a chair conformation and down when the sugar is shown in a Haworth projection; the β-position is equatorial when a sugar is shown in a chair conformation and up when the sugar is shown in a Haworth projection.
- Six-membered ring sugars are **pyranoses;** five-membered ring sugars are **furanoses.**
- The most abundant monosaccharide in nature is D-glucose. All the OH groups in β-D-glucose are in equatorial positions.
- A cyclic hemiacetal can react with an alcohol to form an acetal, called a **glycoside.** If the name “pyranose” or “furanose” is used, the acetal is called a **pyranoside** or a **furanoside,** respectively.
- The bond between the anomeric carbon and the alkoxy oxygen is called a **glycosidic bond.**
- **Disaccharides** consist of two monosaccharides hooked together by a glycosidic linkage. Maltose has an **α-1,4′-glycosidic linkage** between two glucose subunits; cellobiose has a **β-1,4′-glycosidic linkage** between two glucose subunits.
- The most common disaccharide is sucrose; it has a D-glucose subunit and a D-fructose subunit linked by their anomeric carbons.
- **Oligosaccharides** contain 3 to 10 and **polysaccharides** contain as few as 10 or as many as several thousand monosaccharides joined together by glycosidic linkages.
- Starch is composed of amylose and amylopectin. Amylose has unbranched chains of D-glucose units joined by α-1,4′-glycosidic linkages.
- Amylopectin, too, has chains of D-glucose units joined by α-1,4′-glycosidic linkages, but it also has α-1,6′-glycosidic linkages that create branches. Glycogen is similar to amylopectin but has more branches.
- Cellulose has unbranched chains of D-glucose units joined by β-1,4′-glycosidic linkages.
- The α-linkages cause amylose to form a helix and be water soluble; the β-linkages allow the molecules of cellulose to form linear arrays and be water insoluble.
- The surfaces of many cells contain short oligosaccharides that allow the cells to interact with each other. The oligosaccharides are attached to the cell surface by protein groups.
- Proteins bonded to oligosaccharides are called **glycoproteins.**

SUMMARY OF REACTIONS

1. Epimerization (Section 16.5). The mechanism of the reaction is shown on page 558.

2. Enediol rearrangement (Section 16.5). The mechanism of the reaction is shown on page 559.

3. Hemiacetal formation (Section 16.6)

4. Glycoside formation (Section 16.8). The mechanism of the reaction is shown on page 565.

PROBLEMS

18. Name the epimers of L-galactose.

19. Answer the following questions about the aldohexoses:
a. Are D-glucose and D-allose enantiomers? **b.** Are D-idose and D-mannose C-2 epimers?

20. Reduce the carbonyl group of each of the eight D-aldohexoses with $NaBH_4$ and protonate each of the products with HCl. Which of the products is optically active? (*Hint:* An optically active compound does not have a plane of symmetry.)

21. When D-tagatose is added to a basic aqueous solution, an equilibrium mixture of monosaccharides is obtained, two of which are aldohexoses and two of which are ketohexoses. Identify the aldohexoses and ketohexoses.

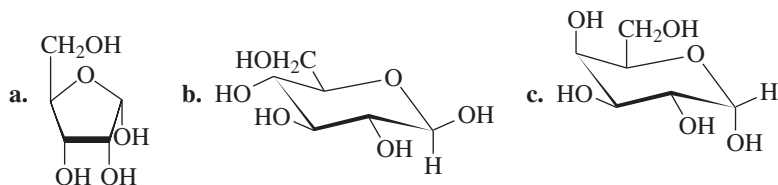
22. If the specific rotation of α-L-galactose is +104.4, what is the specific rotation of α-D-galactose?

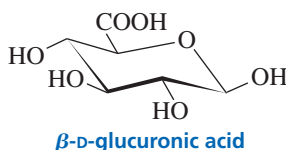
23. The reaction of D-xylose with one equivalent of ethanol plus HCl forms four products. Draw the products.

24. Do fructose, galactose, and cellulose undergo mutarotation?

25. In order to synthesize D-galactose, a student went to the stockroom to get some D-lyxose to use as a starting material. She found that the labels had fallen off the bottles containing D-lyxose and D-xylose. How could she determine which bottle contains D-lyxose? (*Hint:* See Problem 20.)

26. Name the following compounds:

a. **b.** **c.**

27. Hydrolyze each of the compounds in Problem 26 under acidic conditions. In each case, cyclic and a straight-chain monosaccharide will be obtained. Draw the straight-chain monosaccharide in a Fischer projection.

28. D-Glucuronic acid is found widely in plants and animals. One of its functions is to detoxify poisonous HO-containing compounds by reacting with them in the liver to form glucuronides. Glucuronides are water soluble and therefore readily excreted. After ingestion of a poison such as turpentine or phenol, the glucuronides of these compounds are found in the urine. Draw the structure of the α- and β-glucuronides formed by the reaction of β-D-glucuronic acid and phenol.

β-D-glucuronic acid

29. Hyaluronic acid, a component of connective tissue, is known as nature's moisturizer. It is the fluid that lubricates joints and muscles. It is a polymer of alternating *N*-acetyl-D-glucosamine and D-glucuronic acid subunits joined by β-1,3$'$-glycosidic linkages. Draw a short segment of hyaluronic acid.

30. Chondroitin sulfate provides much of the resistance to compression in cartilage. It is similar to hyaluronic acid except that is has a sulfate OSO_3^- group at the 6-position of the *N*-acetyl-D-glucosamine subunit. Draw a short segment of chondroitin sulfate.

31. A student isolated a monosaccharide and determined that it had a molecular weight of 150. Much to his surprise, he found that it was not optically active. What is the structure of the monosaccharide?

32. Propose a mechanism for the formation of D-allose from D-glucose in a basic solution.

33. Draw the mechanism for the interconversion of α-D-glucose and β-D-glucose in dilute HCl.

34. Draw each of the following compounds:

a. β-D-talopyranose **c.** α-D-tagatopyranose **e.** β-L-talopyranose
b. α-D-idopyranose **d.** β-D-psicofuranose **f.** α-L-tagatopyranose

35. When D-fructose is dissolved in D_2O and the solution is made basic, the D-fructose recovered from the solution has an average of 1.7 deuterium atoms attached to the C-1 carbon per molecule. Show the mechanism that accounts for the incorporation of these deuterium atoms into D-fructose.

36. Draw the mechanism for the formation of β-maltose from α-D-galactose and β-D-glucose in dilute HCl.

37. Explain why the C-3 OH group of vitamin C is more acidic than the C-2 OH group.

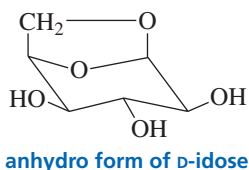
38. Draw the mechanism for the acid-catalyzed hydrolysis of β-maltose.

39. Calculate the percentages of α-D-glucose and β-D-glucose present at equilibrium from the specific rotations of α-D-glucose, β-D-glucose, and the equilibrium mixture. Compare your values with those given in Section 16.6. (*Hint:* The specific rotation of the mixture equals the specific rotation of α-D-glucose times the fraction of glucose present in the α-form plus the specific rotation of β-D-glucose times the fraction of glucose present in the β-form.)

40. Predict whether D-altrose exists preferentially as a pyranose or a furanose. (*Hint:* In the most stable arrangement for a five-membered ring, all the adjacent substituents are trans.)

41. When a pyranose is in the chair conformation in which the CH_2OH group and the C-1 OH group are both in axial positions, the two groups can react to form an acetal. This is called the anhydro form of the sugar (it has "lost water"). The anhydro form of D-idose is shown here. Explain why about 80% of D-idose exists in the anhydro form in an aqueous solution at 100 °C , but only about 0.1% of D-glucose exists in the anhydro form under the same conditions.

anhydro form of D-idose

17

The Organic Chemistry of Amino Acids, Peptides, and Proteins

Cobwebs, silk, muscles, and wool are all proteins. In this chapter, you will find out why muscles and wool can be stretched but cobwebs and silk cannot. You also will see how a reduction reaction followed by an oxidation reaction can alter the structure of hair (another protein) from straight to curly or from curly to straight.

The three kinds of polymers prevalent in nature are polysaccharides, proteins, and nucleic acids. We have just looked at polysaccharides (Section 16.10); now we will turn our attention to proteins and the structurally similar, but shorter, peptides. (Nucleic acids are discussed in Chapter 21.)

Peptides and **proteins** are polymers of amino acids. The amino acids are linked together by amide bonds. An **amino acid** is a carboxylic acid with a protonated amino group on the α-carbon.

$$\mathrm{R{-}CH(\overset{+}{N}H_3){-}C({=}O)OH}$$

a protonated
α-aminocarboxylic acid
an amino acid

$$\mathrm{H_3\overset{+}{N}CH(R){-}C({=}O){-}NHCH(R'){-}C({=}O){-}NHCH(R''){-}C({=}O)O^-}$$

amide bonds

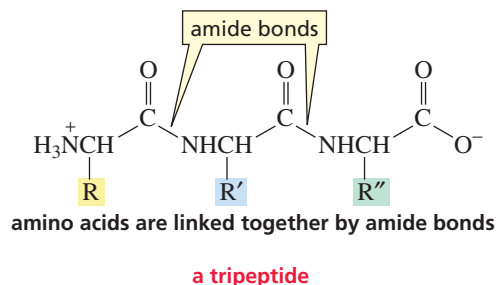
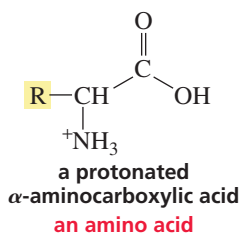
amino acids are linked together by amide bonds
a tripeptide

Amino acid polymers can be composed of any number of amino acids. A **dipeptide** contains two amino acids linked together, a **tripeptide** contains three, an **oligopeptide** contains 4 to 10, and a **polypeptide** contains many. Proteins are naturally occurring polypeptides made up of 40 to 4000 amino acids. Proteins serve many functions in living systems (Table 17.1).

Table 17.1 Examples of the Diverse Functions of Proteins in Living Systems

Structural proteins	These proteins impart strength to biological structures or protect organisms from their environment. For example, collagen is the major component of bones, muscles, and tendons; keratin is the major component of hair, hooves, feathers, fur, and the outer layer of skin.
Protective proteins	Snake venoms and plant toxins are proteins that protect their owners from predators. Blood-clotting proteins protect the vascular system when it is injured. Antibodies and peptide antibiotics protect us from disease.
Enzymes	Enzymes are proteins that catalyze the reactions that occur in cells.
Hormones	Some hormones, compounds that regulate the reactions that occur in living systems, are proteins.
Proteins with physiological functions	These proteins include those that transport and store oxygen in the body, store oxygen in the muscles, and contract muscles.

Proteins can be classified as either fibrous or globular. **Fibrous proteins** contain long chains of polypeptides arranged in threadlike bundles; these proteins are insoluble in water. **Globular proteins** tend to have roughly spherical shapes and most are soluble in water. All structural proteins are fibrous proteins; most enzymes are globular proteins.

17.1 THE NOMENCLATURE OF AMINO ACIDS

The structures of the 20 most common naturally occurring amino acids and the frequency with which each occurs in proteins are shown in Table 17.2. Other amino acids occur in nature but only infrequently. Notice that the amino acids differ only in the substituent (R) that is attached to the α-carbon. The wide variation in these substituents (called **side chains**) is what gives proteins their great structural diversity and, as a consequence, their great functional diversity. Notice too that all amino acids except proline contain a primary amino group. Proline contains a secondary amino group incorporated into a five-membered ring.

Table 17.2 The Most Common Naturally Occurring Amino Acids Shown in the Form that Predominates at Physiological pH (7.4)

	Formula	Name	Abbreviations		Average relative abundance in proteins
Aliphatic side-chain amino acids	$H-CH(^{+}NH_3)-C(=O)O^-$	Glycine	Gly	G	7.5%
	$CH_3-CH(^{+}NH_3)-C(=O)O^-$	Alanine	Ala	A	9.0%
	$CH_3CH(CH_3)-CH(^{+}NH_3)-C(=O)O^-$	Valine*	Val	V	6.9%

(continued)

	Formula	Name	Abbreviations		Average relative abundance in proteins
	$CH_3CH(CH_3)CH_2-CH(^{+}NH_3)-COO^-$	Leucine*	Leu	L	7.5%
	$CH_3CH_2CH(CH_3)-CH(^{+}NH_3)-COO^-$	Isoleucine*	Ile	I	4.6%
Hydroxy-containing amino acids	$HOCH_2-CH(^{+}NH_3)-COO^-$	Serine	Ser	S	7.1%
	$CH_3CH(OH)-CH(^{+}NH_3)-COO^-$	Threonine*	Thr	T	6.0%
Sulfur-containing amino acids	$HSCH_2-CH(^{+}NH_3)-COO^-$	Cysteine	Cys	C	2.8%
	$CH_3SCH_2CH_2-CH(^{+}NH_3)-COO^-$	Methionine*	Met	M	1.7%
Acidic amino acids	$^{-}OOC-CH_2-CH(^{+}NH_3)-COO^-$	Aspartate (aspartic acid)	Asp	D	5.5%
	$^{-}OOC-CH_2CH_2-CH(^{+}NH_3)-COO^-$	Glutamate (glutamic acid)	Glu	E	6.2%
Amides of acidic amino acids	$H_2NC(=O)-CH_2-CH(^{+}NH_3)-COO^-$	Asparagine	Asn	N	4.4%

	Formula	Name	Abbreviations		Average relative abundance in proteins
	$H_2N-C(=O)-CH_2CH_2-CH(^+NH_3)-C(=O)O^-$	Glutamine	Gln	Q	3.9%
Basic amino acids	$H_3\overset{+}{N}CH_2CH_2CH_2CH_2-CH(^+NH_3)-C(=O)O^-$	Lysine*	Lys	K	7.0%
	$H_2N-C(=\overset{+}{N}H_2)-NHCH_2CH_2CH_2-CH(^+NH_3)-C(=O)O^-$	Arginine*	Arg	R	4.7%
Benzene-containing amino acids	$C_6H_5-CH_2-CH(^+NH_3)-C(=O)O^-$	Phenylalanine*	Phe	F	3.5%
	$HO-C_6H_4-CH_2-CH(^+NH_3)-C(=O)O^-$	Tyrosine	Tyr	Y	3.5%
Heterocyclic amino acids	pyrrolidine ring, $\overset{+}{N}(H)(H)$, $-C(=O)O^-$	Proline	Pro	P	4.6%
	imidazole ring (N, NH)$-CH_2-CH(^+NH_3)-C(=O)O^-$	Histidine*	His	H	2.1%
	indole ring (NH)$-CH_2-CH(^+NH_3)-C(=O)O^-$	Tryptophan*	Trp	W	1.1%

*Essential amino acid

The amino acids are always called by their common names. Often, the name tells you something about the amino acid. For example, glycine got its name from its sweet taste (*glykos* is Greek for "sweet"), and valine, like valeric acid, has five carbons. Asparagine was first found in asparagus, and tyrosine was isolated from cheese (*tyros* is Greek for "cheese").

Notice that, in spite of its name, isoleucine has a *sec*-butyl substituent, not an isobutyl substituent. Leucine is the amino acid that has an isobutyl substituent. Each of the amino acids has both a three-letter abbreviation (in most cases, the first three letters of the name) and a single-letter abbreviation.

glycine

Proline, histidine, and tryptophan are heterocyclic amino acids. We have noted that proline, with its nitrogen incorporated into a five-membered ring, is the only amino acid that contains a secondary amino group. Histidine is an imidazole-substituted alanine. Imidazole is an aromatic compound because it is cyclic and planar, each of its ring atoms has a p orbital, and it has three pairs of delocalized π electrons (Section 7.14). The pK_a of a protonated imidazole ring is 6.0, so the ring can exist in both the acidic form and the basic form at physiological pH (7.4).

Tryptophan is an indole-substituted alanine. Like imidazole, indole is an aromatic compound. Because the lone pair on the nitrogen of indole is needed for the compound's aromaticity, indole is a very weak base. (The pK_a of protonated indole is −2.4.) Therefore, the ring nitrogen in tryptophan is never protonated under physiological conditions.

leucine

The 10 amino acids denoted in Table 17.2 by asterisks (*) are **essential amino acids.** Humans must obtain them from their diet because they either cannot synthesize them at all or cannot synthesize them in adequate amounts. For example, humans must have a dietary source of phenylalanine because they cannot synthesize benzene rings. However, they do not need tyrosine in their diet because they can synthesize it from phenylalanine (Section 19.7). Although humans can synthesize arginine, it is needed for growth in greater amounts than can be synthesized. So arginine is considered an essential amino acid for children but not for adults.

Proteins and Nutrition

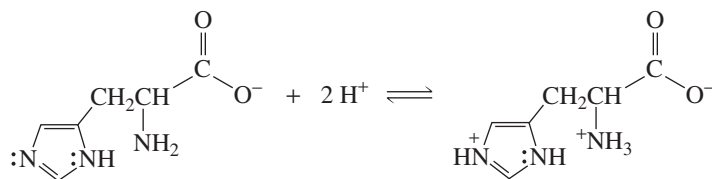
Proteins are an important component of our diets. Dietary protein is hydrolyzed in the body to individual amino acids. Some of these amino acids are used to synthesize proteins needed by the body, some are broken down (metabolized) to supply energy to the body, and some are used as starting materials for the synthesis of nonprotein compounds that the body needs, such as thyroxine (Section 7.17), adrenaline, and melanin (Section 19.7).

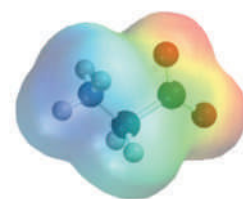
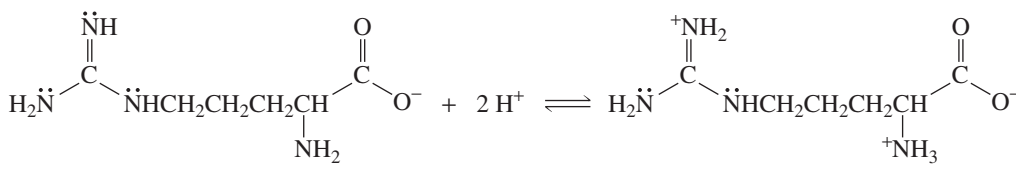
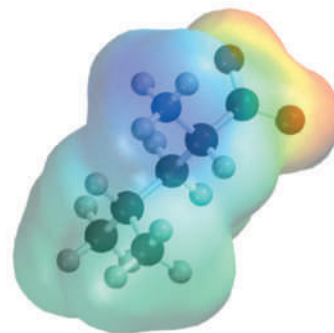
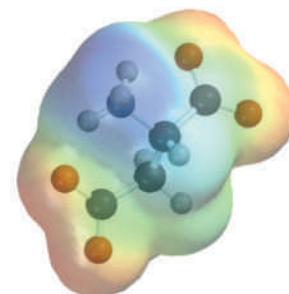
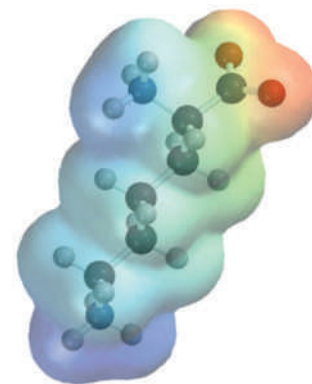
Complete proteins (meat, fish, eggs, and milk) contain all 10 essential amino acids. Incomplete proteins contain too little of one or more essential amino acids to support human growth. For example, beans and peas are deficient in methionine, corn is deficient in lysine and tryptophan, and rice is deficient in lysine and threonine. Vegetarians, therefore, must have a diet that includes proteins from different sources.

aspartate

PROBLEM 1

a. Explain why, when the imidazole ring of histidine is protonated, the double-bonded nitrogen is the nitrogen that accepts the proton. (*Hint*: Localized electrons are more apt to be protonated than delocalized electrons.)

$$\text{(imidazolyl)}CH_2CH(NH_2)COO^- + 2\,H^+ \rightleftharpoons \text{(protonated imidazolyl, } HN^+\text{)}CH_2CH(^+NH_3)COO^-$$

b. Explain why, when the guanidino group of arginine is protonated, the double-bonded nitrogen is the nitrogen that accepts the proton.

$$H_2N{-}C({=}NH){-}NHCH_2CH_2CH_2CH(NH_2)COO^- + 2\,H^+ \rightleftharpoons H_2N{-}C({=}^+NH_2){-}NHCH_2CH_2CH_2CH(^+NH_3)COO^-$$

lysine

17.2 THE CONFIGURATION OF AMINO ACIDS

The α-carbon of all the naturally occurring amino acids (except glycine) is an asymmetric center. Therefore, 19 of the 20 amino acids listed in Table 17.2 can exist as enantiomers. The D and L notation used for monosaccharides (Section 16.2) is also used for amino acids.

Naturally occurring monosaccharides have the D configuration.

Naturally occurring amino acids have the L configuration.

An amino acid drawn in a Fischer projection with the carboxyl group at the top and the R group at the bottom of the vertical axis is a **D-amino acid** if the amino group is on the right and an **L-amino acid** if the amino group is on the left. Unlike monosaccharides, in which the D isomer is the one found in nature, most amino acids found in nature have the L configuration. To date, D-amino acids have been found only in a few peptide antibiotics and in some small peptides attached to the cell walls of bacteria. (You will see how an L-amino acid can be converted to a D-amino acid in Section 18.11.)

L-alanine
an amino acid

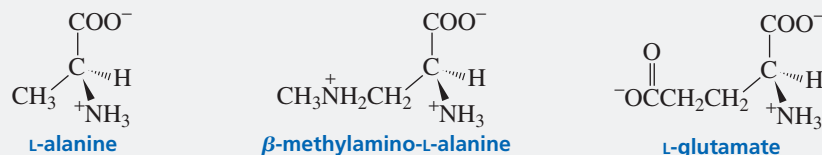
Why D-sugars and L-amino acids? Although it made no difference which isomer nature "selected" to be synthesized, it was important that only one was selected. For example, proteins that contain both D- and L-amino acids do not fold properly, and without proper folding there can be no catalysis (Section 17.12). It was also important that the same isomer be synthesized by all organisms. For example, because mammals have L-amino acids, L-amino acids must be the isomers synthesized by the organisms that mammals depend on for food.

Amino Acids and Disease

The Chamorro people of Guam have a high incidence of a syndrome that resembles amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) with elements of Parkinson's disease and dementia. This syndrome developed during World War II when, as a result of food shortages, the tribe ate large quantities of *Cycas micronesica* seeds. These seeds contain β-methylamino-L-alanine, an amino acid that binds to cell receptors that bind L-glutamate. When monkeys are given β-methylamino-L-alanine, they develop some of the features of this syndrome. There is hope that, by studying the mechanism of action of β-methylamino-L-alanine, we may gain an understanding of how ALS and Parkinson's disease arise.

COO^-, CH_3, H, $^+NH_3$
L-alanine

COO^-, $CH_3\overset{+}{N}H_2CH_2$, H, $^+NH_3$
β-methylamino-L-alanine

COO^-, $^-OC(=O)CH_2CH_2$, H, $^+NH_3$
L-glutamate

PROBLEM 2♦

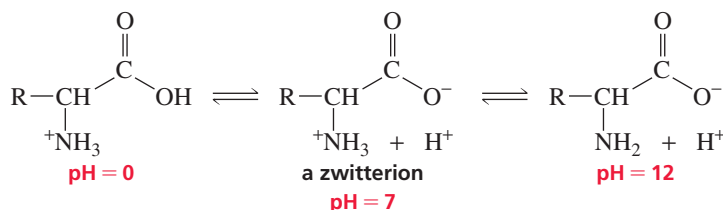
Which amino acids in Table 17.2 have more than one asymmetric center?

17.3 THE ACID–BASE PROPERTIES OF AMINO ACIDS

Every amino acid has a carboxyl group and an amino group, and each group can exist in an acidic form or a basic form, depending on the pH of the solution in which the amino acid is dissolved.

We have seen that compounds exist primarily in their acidic forms (that is, with their protons attached) in solutions that are more acidic than their pK_a values, and primarily in their basic forms (that is, without their protons) in solutions that are more basic than their pK_a values (Section 2.10).

$$R-CH(\overset{+}{N}H_3)-C(=O)OH \rightleftharpoons R-CH(\overset{+}{N}H_3)-C(=O)O^- + H^+ \rightleftharpoons R-CH(NH_2)-C(=O)O^- + H^+$$

pH = 0 — a zwitterion, pH = 7 — pH = 12

The acidic form (with the proton) predominates if the pH of the solution is less than the pK_a of the ionizable group, and the basic form (without the proton) predominates if the pH of the solution is greater than the pK_a of the ionizable group.

The carboxyl groups of the amino acids have pK_a values of approximately 2, and the protonated amino groups have pK_a values near 9 (Table 17.3). Both groups, therefore, will be in their acidic forms in a very acidic solution (pH ~ 0). At pH = 7, the pH of the solution is greater than the pK_a of the carboxyl group, but less than the pK_a of the protonated amino group, so the carboxyl group will be in its basic form and the amino group will be in its acidic form. In a strongly basic solution (pH ~ 12), both groups will be in their basic forms.

Table 17.3 The pK_a Values of Amino Acids

Amino acid	pK_a α-COOH	pK_a α-$\overset{+}{N}H_3$	pK_a Side chain
Alanine	2.34	9.69	—
Arginine	2.17	9.04	12.48
Asparagine	2.02	8.84	—
Aspartic acid	2.09	9.82	3.86
Cysteine	1.92	10.46	8.35
Glutamic acid	2.19	9.67	4.25
Glutamine	2.17	9.13	—
Glycine	2.34	9.60	—
Histidine	1.82	9.17	6.04
Isoleucine	2.36	9.68	—
Leucine	2.36	9.60	—
Lysine	2.18	8.95	10.79
Methionine	2.28	9.21	—
Phenylalanine	2.16	9.18	—
Proline	1.99	10.60	—
Serine	2.21	9.15	—
Threonine	2.63	9.10	—
Tryptophan	2.38	9.39	—
Tyrosine	2.20	9.11	10.07
Valine	2.32	9.62	—

Notice that an amino acid can never exist as an uncharged compound, regardless of the pH of the solution. To be uncharged, an amino acid would have to lose a proton from an $^+NH_3$ group with a pK_a of about 9 before it would lose a proton from a COOH group with a pK_a of about 2. This is impossible because a weak acid ($pK_a = 9$) cannot lose a proton easier than a strong acid ($pK_a = 2$) can. Therefore, at physiological pH (7.4), an amino

acid exists as a dipolar ion, called a zwitterion. A **zwitterion** is a compound that has a negative charge on one atom and a positive charge on a nonadjacent atom. (The name comes from *zwitter*, German for "hermaphrodite" or "hybrid.")

PROBLEM 3

Explain why amino acids, unlike most amines and carboxylic acids, are insoluble in diethyl ether.

PROBLEM 4♦

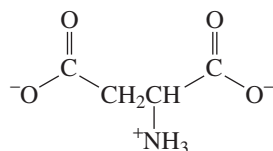
Why are the carboxylic acid groups of the amino acids more acidic ($pK_a \sim 2$) than a carboxylic acid such as acetic acid ($pK_a = 4.76$)?

PROBLEM 5 Solved

Draw the predominant form for each of the following amino acids at physiological pH (7.4):

a. aspartate
b. histidine
c. glutamine
d. lysine
e. arginine
f. tyrosine

Solution to 5a Both carboxyl groups are in their basic forms because the pH of the solution is greater than their pK_a values. The protonated amino group is in its acidic form because the pH of the solution is less than its pK_a value.

$$^{-}O-C(=O)-CH_2CH(^{+}NH_3)-C(=O)-O^{-}$$

PROBLEM 6♦

Draw the predominant form for glutamate in a solution with the following pH:

a. 0 **b.** 3 **c.** 6 **d.** 11

17.4 THE ISOELECTRIC POINT

The **isoelectric point** (pI) of an amino acid is the pH at which it has no net charge. In other words, it is the pH at which the amount of positive charge on an amino acid exactly balances the amount of negative charge:

pI = pH at which there is no net charge

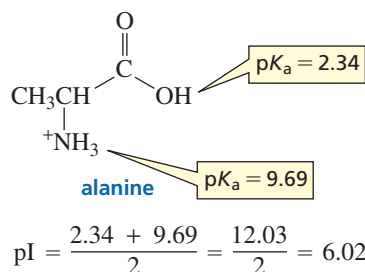
The pI of an amino acid that does *not have an ionizable side chain*—such as alanine—is midway between its two pK_a values.

$$CH_3CH(^{+}NH_3)-C(=O)-OH$$

$pK_a = 2.34$ (COOH)

$pK_a = 9.69$ ($^{+}NH_3$)

alanine

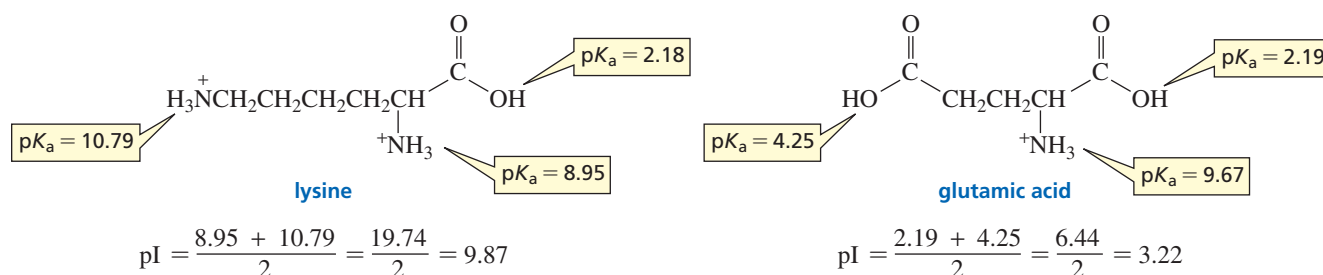
$$pI = \frac{2.34 + 9.69}{2} = \frac{12.03}{2} = 6.02$$

The pI of most amino acids (see Problem 51) that *have an ionizable side chain* is the average of the pK_a values of the similarly ionizing groups (either positively charged groups ionizing to uncharged groups or uncharged groups ionizing to negatively charged groups). For example, the pI of lysine is the average of the pK_a values of the two groups that are positively charged in their acidic form and uncharged in their basic form.

The pI of glutamic acid, on the other hand, is the average of the pK_a values of the two groups that are uncharged in their acidic form and negatively charged in their basic form.

$H_3\overset{+}{N}CH_2CH_2CH_2CH_2CH(\overset{+}{N}H_3)COOH$ — lysine: $pK_a = 10.79$ ($\overset{+}{N}H_3$ of side chain), $pK_a = 2.18$ (COOH), $pK_a = 8.95$ (α-$\overset{+}{N}H_3$)

$HOOCCH_2CH_2CH(\overset{+}{N}H_3)COOH$ — glutamic acid: $pK_a = 4.25$ (side-chain COOH), $pK_a = 2.19$ (COOH), $pK_a = 9.67$ ($\overset{+}{N}H_3$)

$$\text{pI} = \frac{8.95 + 10.79}{2} = \frac{19.74}{2} = 9.87$$

$$\text{pI} = \frac{2.19 + 4.25}{2} = \frac{6.44}{2} = 3.22$$

PROBLEM 7♦

Calculate the pI of each of the following amino acids:

a. asparagine **b.** arginine **c.** serine **d.** aspartate

PROBLEM 8♦

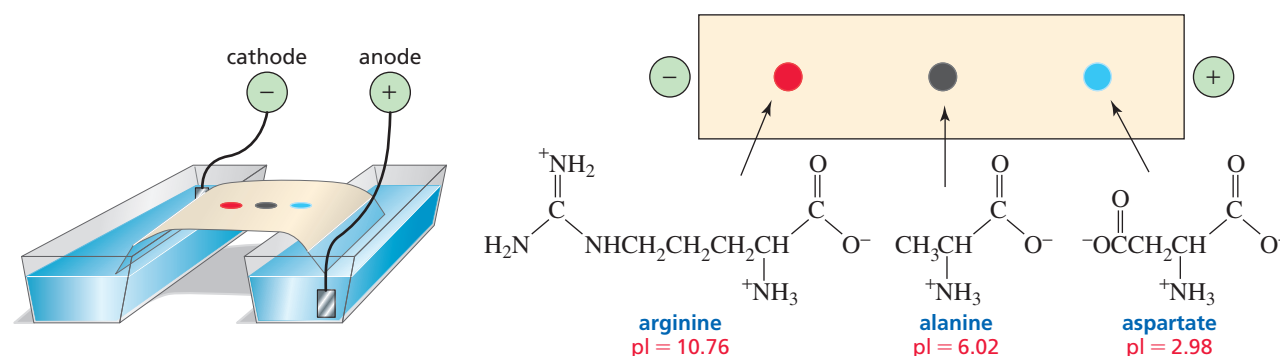
a. Which amino acid has the lowest pI value? **b.** Which amino acid has the highest pI value?

17.5 SEPARATING AMINO ACIDS

A mixture of amino acids can be separated by several different techniques. Electrophoresis and ion-exchange chromatography are two such techniques.

Electrophoresis

Electrophoresis separates amino acids on the basis of their pI values. A few drops of a solution of an amino acid mixture are applied to the middle of a piece of filter paper (or to a gel). When the paper (or the gel) is placed in a buffered solution between two electrodes and an electric field is applied (Figure 17.1), an amino acid with a pI greater than the pH of the solution will have an overall *positive charge* and will migrate toward the *cathode (the negative electrode)*.

An amino acid will be positively charged if the pH of the solution is less than the pI of the amino acid, and it will be negatively charged if the pH of the solution is greater than the pI of the amino acid.

▲ **Figure 17.1**
Arginine, alanine, and aspartate are separated by electrophoresis at pH = 5.

The farther an amino acid's pI is from the pH of the solution, the more positive the amino acid will be and the farther it will migrate toward the cathode in a given amount of time. An amino acid with a pI less than the pH of the solution will have an overall *negative charge* and will migrate toward the *anode (the positive electrode)*. If two molecules have the same charge, the larger one will move more slowly during electrophoresis because the same charge has to move a greater mass.

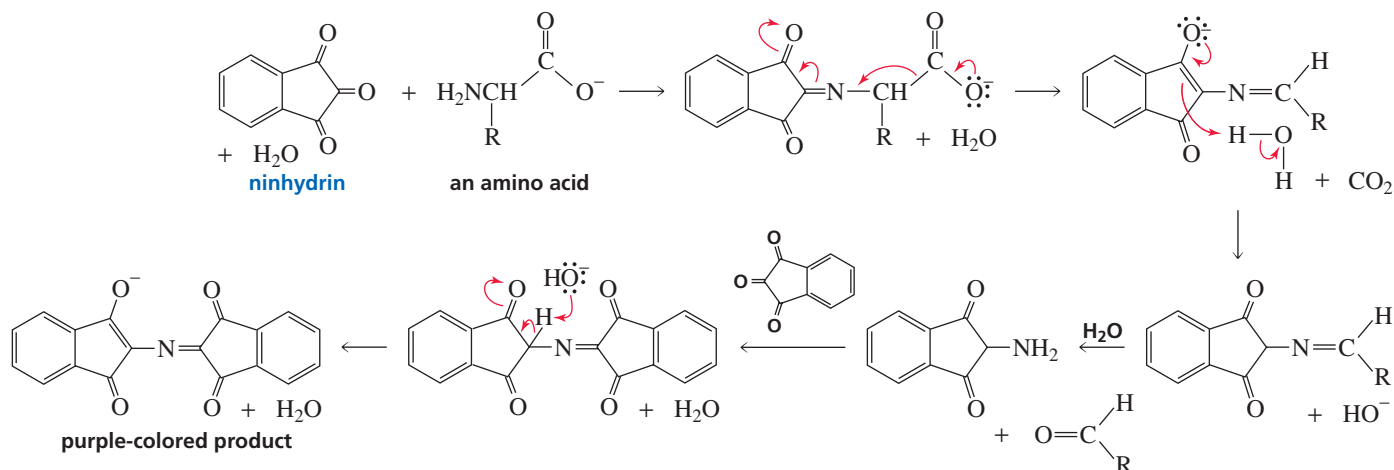
Considering that amino acids are colorless, how can we detect them after they have been separated? After the amino acids have been separated by electrophoresis, the filter paper is painted with a solution of ninhydrin and dried in a warm oven. Most amino acids form a purple product when heated with ninhydrin. The number of amino acids in the mixture is determined by the number of colored spots on the filter paper. The individual amino acids can be identified by their location on the paper compared with a standard.

STEPS IN THE REACTION OF AN AMINO ACID WITH NINHYDRIN TO FORM A COLORED PRODUCT

ninhydrin + H_2O + an amino acid ($H_2NCH(R)CO_2^-$) → imine + H_2O → + CO_2 → (tautomerization) → + HO^- → (H_2O) ninhydrin-amine (NH_2) + $O{=}C(H)R$ → (+ ninhydrin) → + H_2O → purple-colored product + H_2O

ninhydrin

an amino acid

purple-colored product

- The ketone reacts with the amino acid to form an imine.
- Decarboxylation occurs because the electrons left behind can be delocalized onto an oxygen.
- Tautomerization followed by hydrolysis of the imine forms the deaminated amino acid and a ninhydrin-amine.
- Reaction of this amine with another molecule of ninhydrin forms an imine. Loss of a proton forms a highly conjugated (colored) product (Section 10.17).

Painting a paper with a solution of ninhydrin allows latent fingerprints (as a consequence of amino acids left behind by the fingers) to be developed.

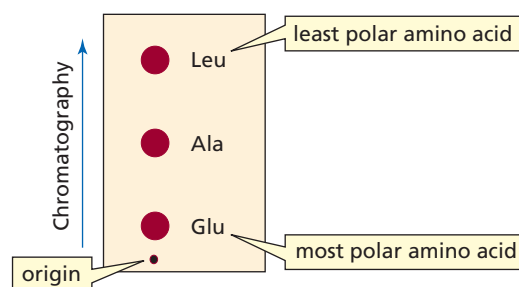
PROBLEM 9♦

What aldehyde is formed when valine is treated with ninhydrin?

Paper/Thin-Layer Chromatography

Paper chromatography once played an important role in biochemical analysis because it provided a method for separating amino acids using very simple equipment. Although more modern techniques are generally employed today, we will describe the principles behind paper chromatography because many of the same principles are employed in modern separation techniques.

Paper chromatography separates amino acids on the basis of polarity. A few drops of a solution of an amino acid mixture are applied to the bottom of a strip of filter paper. The edge of the paper is then placed in a solvent. The solvent moves up the paper by capillary action, carrying the amino acids with it. Depending on their polarities, the amino acids have different affinities for the mobile (solvent) and stationary (paper) phases and, therefore, some travel up the paper farther than others.

When a solvent is used that is less polar than the paper, the more polar the amino acid, the more strongly it is adsorbed onto the relatively polar paper. The less polar amino acids travel farther up the paper since they have a greater affinity for the less polar mobile phase. Therefore, when the paper is developed with ninhydrin, the colored spot closest to the origin is the most polar amino acid and the spot farthest away from the origin is the least polar amino acid (Figure 17.2).

Less polar amino acids travel more rapidly if the solvent is less polar than the paper.

◀ **Figure 17.2**
Separation of glutamate, alanine, and leucine by paper chromatography.

The most polar amino acids are those with charged side chains, the next most polar are those with side chains that can form hydrogen bonds, and the least polar are those with hydrocarbon side chains. For amino acids with hydrocarbon side chains, the polarity of the amino acid decreases as the size of the alkyl group increases. In other words, leucine [$R = –CH_2CH(CH_3)_2$] is less polar than valine [$R = –CH(CH_3)_2$].

Paper chromatography has largely been replaced by **thin-layer chromatography** (TLC), which differs from paper chromatography in that TLC uses a plate with a coating of solid material instead of filter paper. How the amino acids separate depends on the solid material and the solvent chosen for the mobile phase.

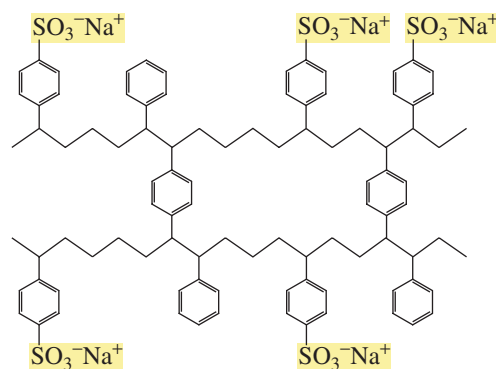
Chromatography separates amino acids based on their polarity, and electrophoresis separates them based on their charge. The two techniques can be applied on the same piece of filter paper to give a two-dimensional separation (that is, the amino acids are separated according to both their polarity and their charge. (See Problems 38 and 57.)

PROBLEM 10

A mixture of seven amino acids (glycine, glutamate, leucine, lysine, alanine, isoleucine, and aspartate) is separated by chromatography. Explain why only six spots show up when the chromatographic plate is coated with ninhydrin and heated.

Ion-Exchange Chromatography

A technique called **ion-exchange chromatography** is able to both separate and identify amino acids and determine the relative amount of each amino acid in a mixture. This technique employs a column packed with an insoluble resin. A solution of a mixture of amino acids is loaded onto the top of the column, and a series of buffer solutions are poured through the column. The amino acids separate because they flow through the column at different rates.

The resin is a chemically inert material with charged groups. The structure of a commonly used resin is shown in Figure 17.3. If a mixture of lysine and glutamate in a solution of pH = 6 were to be loaded onto the column, glutamate would travel down the column rapidly because its negatively charged side chain would be repelled by the negatively charged sulfonic acid groups of the resin. The positively charged side chain of lysine, on the other hand, would cause that amino acid to be retained on the column. This kind of resin is called a **cation-exchange resin** because it exchanges the Na^+ counterions of the SO_3^- groups for the positively charged species that is traveling through the column. In addition, the relatively nonpolar nature of the column causes it to retain nonpolar amino acids longer than polar amino acids.

Cations bind strongly to cation-exchange resins.

$SO_3^-Na^+$ $SO_3^-Na^+$ $SO_3^-Na^+$

$SO_3^-Na^+$ $SO_3^-Na^+$

◀ **Figure 17.3**
A section of a cation-exchange resin.

An **amino acid analyzer** is an instrument that automates ion-exchange chromatography. When a solution of amino acids passes through the column of an amino acid analyzer containing a cation-exchange resin, the amino acids move through the column at different rates, depending on their overall charge. The solution that flows out of the column (the effluent) is collected in fractions. These are collected often enough that each amino acid ends up in a single fraction (Figure 17.4).

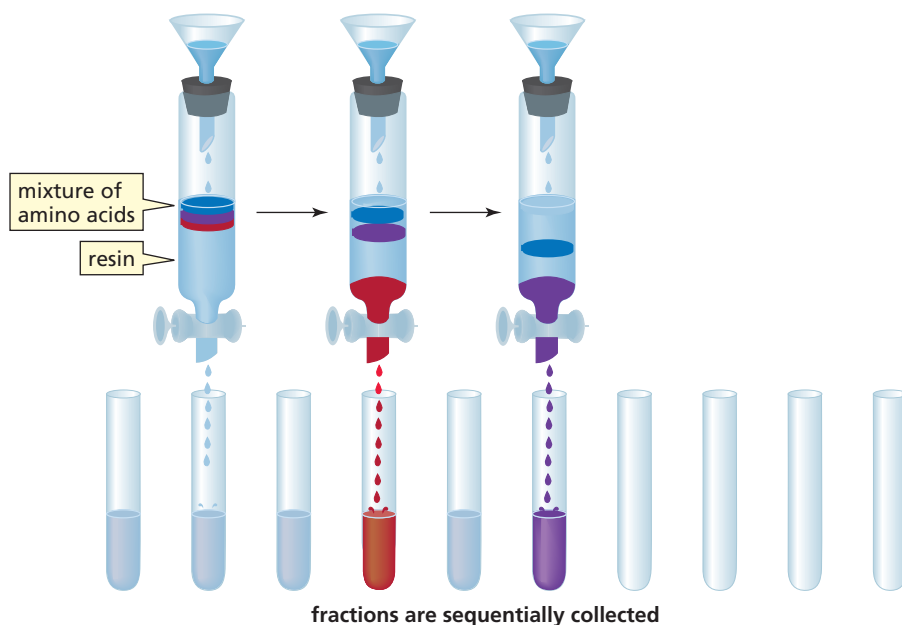



Figure 17.4 Separation of amino acids by ion-exchange chromatography.

If ninhydrin is added to each of the fractions, the concentration of amino acid in each fraction can be determined by the amount of absorbance at 570 nm because the colored compound formed by the reaction of an amino acid with ninhydrin has a λ_{max} of 570 nm (Section 10.17). This information combined with each fraction's rate of passage through the column allows the identity and relative amount of each amino acid in the mixture to be determined (Figure 17.5).

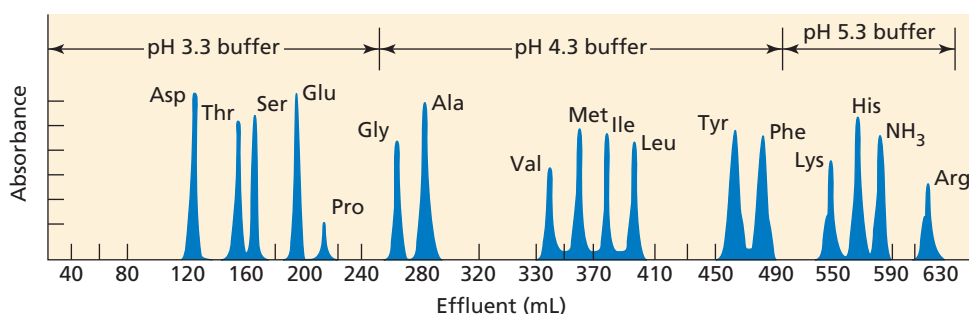



Figure 17.5 A typical chromatogram obtained from the separation of a mixture of amino acids using an automated amino acid analyzer.

Water Softeners: Examples of Cation-Exchange Chromatography

Water-softening systems contain a column packed with a cation-exchange resin that has been flushed with concentrated sodium chloride. When "hard water" (water with high levels of Ca^{2+} and Mg^{2+}; Section 20.3) passes through the column, the resin binds Ca^{2+} and Mg^{2+} more tightly than it binds Na^+. Thus, the water-softening system removes Ca^{2+} and Mg^{2+} from the water and replaces them with Na^+. The resin must be recharged from time to time by being flushed with concentrated sodium chloride, thereby replacing the bound Ca^{2+} and Mg^{2+} with Na^+.

PROBLEM 11

Explain the order of elution (with a buffer of pH 4) of the following pairs of amino acids through a column packed with the cation-exchange resin shown in Figure 17.3:

a. aspartate before serine
b. serine before alanine
c. valine before leucine
d. tyrosine before phenylalanine

PROBLEM 12

Why are buffer solutions of increasingly higher pH used to elute the column that generates the chromatogram shown in Figure 17.5? (*Elute* means "wash out with a solvent.")

17.6 THE SYNTHESIS OF AMINO ACIDS

Chemists do not have to rely on nature to produce amino acids; they can synthesize them in the laboratory, using a variety of methods. Three methods are described here.

Reductive Amination

Amino acids can be synthesized by reductive amination of an α-keto acid (Section 12.8).

$$\mathrm{RC(=O)COOH} \xrightarrow[\text{2. } H_2,\ Pd/C]{\text{1. excess } NH_3,\ \text{trace acid}} \mathrm{RCH(\overset{+}{N}H_3)COO^-}$$

N-Phthalimidomalonic Ester Synthesis

Amino acids can be synthesized with much better yields than those obtained by the previous method via an *N*-phthalimidomalonic ester synthesis.

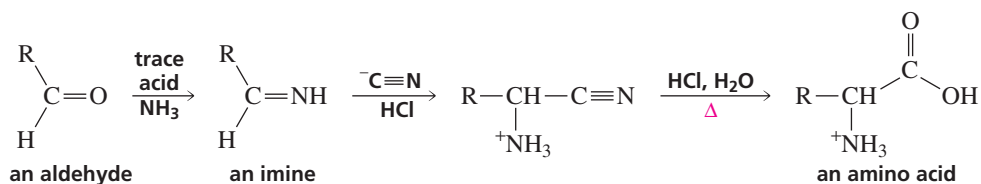
THE STEPS IN THE *N*-PHTHALIMIDOMALONIC ESTER SYNTHESIS

α-bromomalonic ester + potassium phthalimide ⟶ *N*-phthalimidomalonic ester $\xrightarrow{RO^-}$ carbanion + ROH $\xrightarrow{R'-Br}$ alkylated *N*-phthalimidomalonic ester + Br^- $\xrightarrow[\Delta]{HCl,\ H_2O}$ phthalic acid + CO_2 + an amino acid ($H_3\overset{+}{N}CH(R')COOH$)

- α-Bromomalonic ester and potassium phthalimide undergo an S_N2 reaction.
- A proton is easily removed from the α-carbon of *N*-phthalimidomalonic ester because it is flanked by two carbonyl groups (Section 13.1).
- The resulting carbanion undergoes an S_N2 reaction with an alkyl halide.
- Heating in an acidic aqueous solution hydrolyzes the two esters and the two amide bonds and decarboxylates the 3-oxocarboxylic acid (Sections 11.8, 11.12, and 13.9).

Strecker Synthesis

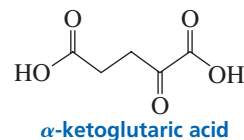
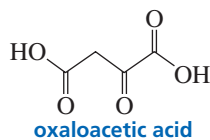
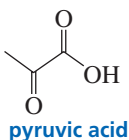
In the Strecker synthesis, an aldehyde reacts with ammonia to form an imine. An addition reaction with cyanide ion forms an intermediate, which, when hydrolyzed, forms the amino acid (Section 12.6).

$$\underset{\text{an aldehyde}}{R(H)C{=}O} \xrightarrow[NH_3]{\text{trace acid}} \underset{\text{an imine}}{R(H)C{=}NH} \xrightarrow[HCl]{^{-}C{\equiv}N} R{-}\underset{^{+}NH_3}{CH}{-}C{\equiv}N \xrightarrow[\Delta]{HCl,\ H_2O} \underset{\text{an amino acid}}{R{-}\underset{^{+}NH_3}{CH}{-}C({=}O)OH}$$

PROBLEM 13♦

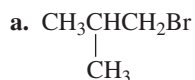
Cells can also convert α-keto acids into amino acids, but because the reagents organic chemists use for this reaction are not available in cells, they carry out this reaction by a different mechanism (Sections 12.8 and 11.13).

a. What amino acid is obtained from the reductive amination of each of the following metabolic intermediates in a cell?

b. What amino acids are obtained from the same compounds when the amino acids are synthesized in the laboratory?

pyruvic acid   oxaloacetic acid   α-ketoglutaric acid

PROBLEM 14♦

What amino acid would be formed using the *N*-phthalimidomalonic ester synthesis when the following alkyl halides are used in the third step?

a. $CH_3CH(CH_3)CH_2Br$ **b.** $CH_3SCH_2CH_2Br$

PROBLEM 15♦

What amino acid would be formed when the aldehyde used in the Strecker synthesis is

a. acetaldehyde?   **b.** 2-methylbutanal?   **c.** 3-methylbutanal?

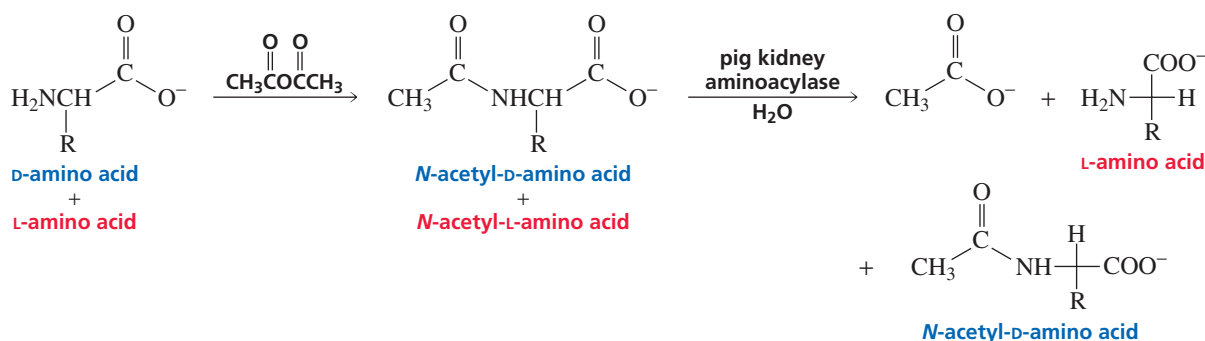
17.7 THE RESOLUTION OF RACEMIC MIXTURES OF AMINO ACIDS

When amino acids are synthesized in nature, only the L-enantiomer is formed (Section 6.7). When amino acids are synthesized in the laboratory, however, the product is a racemic mixture of D and L amino acids. If only one isomer is desired, the enantiomers must be separated, which can be accomplished by means of an enzyme-catalyzed reaction.

Because an enzyme is chiral, it will react at a different rate with each of the enantiomers or derivatives of the enantiomers (Section 6.8). For example, pig kidney aminoacylase is an enzyme that catalyzes the hydrolysis of *N*-acetyl-L-amino acids, but not *N*-acetyl-D-amino acids.

Therefore, if the racemic mixture of amino acids is converted to a pair of *N*-acetyl-amino acids (by a nucleophilic acyl substitution reaction) and the *N*-acetylated mixture is hydrolyzed with pig kidney aminoacylase, then the products will be the L-amino acid and *N*-acetyl-D-amino acid, which are easily separated.

$$H_2NCH(R)CO_2^- \xrightarrow{CH_3COCCH_3\ (\text{acetic anhydride})} CH_3C(=O)NHCH(R)CO_2^- \xrightarrow[H_2O]{\text{pig kidney aminoacylase}} CH_3CO_2^- + H_2N\text{–}C(H)(R)\text{–}COO^- + CH_3C(=O)NH\text{–}C(H)(R)\text{–}COO^-$$

D-amino acid + L-amino acid → N-acetyl-D-amino acid + N-acetyl-L-amino acid → L-amino acid + N-acetyl-D-amino acid

In Section 6.8, we saw that a racemic mixture of amino acids can also be separated by the enzyme D-amino acid oxidase.

PROBLEM 16

Pig liver esterase is an enzyme that catalyzes the hydrolysis of esters. It hydrolyzes esters of L-amino acids more rapidly than esters of D-amino acids. How can this enzyme be used to separate a racemic mixture of amino acids?

17.8 PEPTIDE BONDS AND DISULFIDE BONDS

Peptide bonds and disulfide bonds are the only covalent bonds that join amino acids together in a peptide or a protein.

Peptide Bonds

The amide bonds that link amino acids are called **peptide bonds.** By convention, peptides and proteins are written with the free amino group (of the **N-terminal amino acid**) on the left and the free carboxyl group (of the **C-terminal amino acid**) on the right.

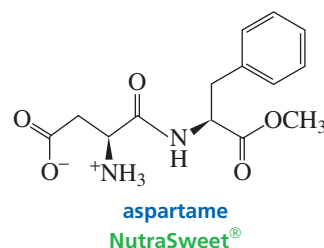
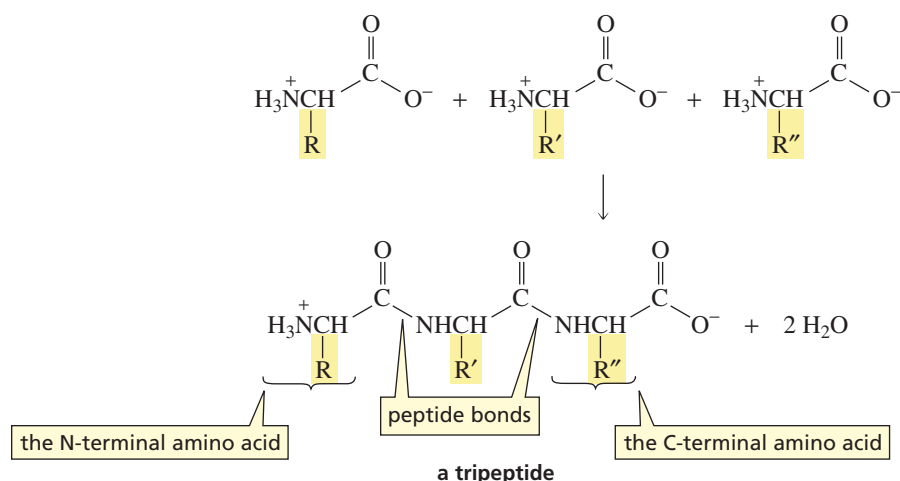
$$H_3\overset{+}{N}CH(R)CO_2^- + H_3\overset{+}{N}CH(R')CO_2^- + H_3\overset{+}{N}CH(R'')CO_2^- \longrightarrow H_3\overset{+}{N}CH(R)C(=O)NHCH(R')C(=O)NHCH(R'')CO_2^- + 2\ H_2O$$

the N-terminal amino acid

peptide bonds

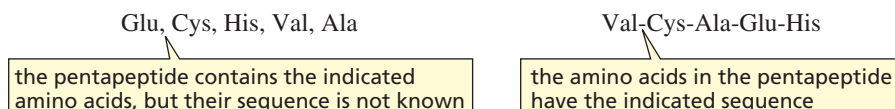
the C-terminal amino acid

a tripeptide

aspartame
NutraSweet®

Aspartame is the methyl ester of a dipeptide of L-aspartate and L-phenylalanine.

When the identities of the amino acids in a peptide are known but their sequence is not, the amino acids are written separated by commas. When their sequence is known, the amino acids are written connected by hyphens. For example, in the pentapeptide represented on the right, valine is the N-terminal amino acid and histidine is the C-terminal amino acid. The amino acids are numbered starting with the N-terminal end. Alanine is, therefore, referred to as Ala 3 because it is the third amino acid from the N-terminal end.

Glu, Cys, His, Val, Ala — the pentapeptide contains the indicated amino acids, but their sequence is not known

Val-Cys-Ala-Glu-His — the amino acids in the pentapeptide have the indicated sequence

A peptide bond has about 40% double-bond character because of electron delocalization (Section 11.2).

α-carbon R α-carbon R

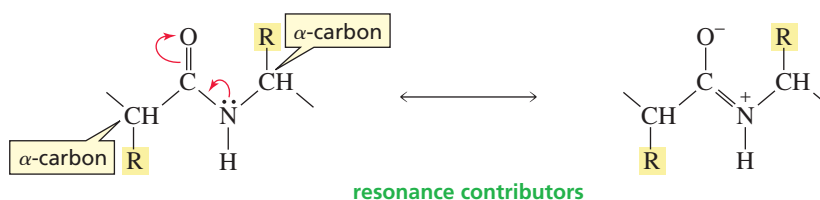
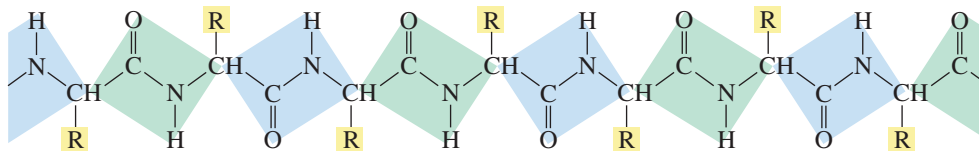
resonance contributors

The partial double-bond character prevents free rotation about the peptide bond, so the carbon and nitrogen atoms of the peptide bond and the two atoms to which each is attached are held rigidly in a plane (Figure 17.6). This regional planarity affects the way a chain of amino acids can fold; this has important implications for the three-dimensional shapes of peptides and proteins (Section 17.12).

Figure 17.6
A segment of a polypeptide chain. Colored squares indicate the plane defined by each peptide bond. Notice that the R groups bonded to the α-carbons are on alternate sides of the peptide backbone.

Runner's High

Several peptide hormones, including β-endorphin, leucine enkephalin, and methionine enkephalin are synthesized by the body to control pain. β-Endorphin has a chain of 31 amino acids, whereas the two enkephalins are pentapeptides. The five amino acids at the N-terminal end of β-endorphin are the same as those in methionine enkephalin (see Problem 55). These peptides control the body's sensitivity to pain by binding to receptors in certain brain cells. Part of the their three-dimensional structures must be similar to that of morphine because they bind to the same receptors. The phenomenon known as "runner's high" that kicks in after vigorous exercise and the relief of pain through acupuncture are thought to be due to the release of these peptides.

Tyr-Gly-Gly-Phe-Leu
leucine enkephalin

Tyr-Gly-Gly-Phe-Met
methionine enkephalin

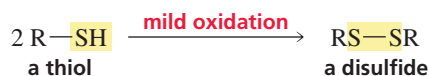
PROBLEM 17
Draw Val-Gly and Gly-Val.

PROBLEM 18
Draw the tetrapeptide Ala-Thr-Asp-Asn and indicate the peptide bonds.

PROBLEM 19
Which bonds in the backbone of a peptide can rotate freely?

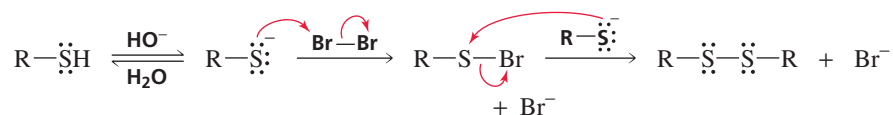
Disulfide Bonds

When thiols are oxidized under mild conditions, they form a **disulfide**—a compound with an S—S bond.

$$2\,R{-}SH \xrightarrow{\text{mild oxidation}} RS{-}SR$$

a thiol → a disulfide

An oxidizing agent commonly used for this reaction is Br_2 in a basic solution.

MECHANISM FOR THE OXIDATION OF A THIOL TO A DISULFIDE

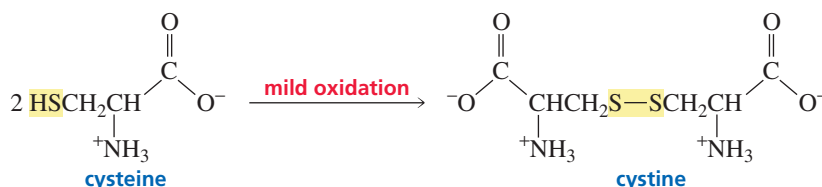
$$R\text{—}\ddot{\underset{..}{S}}H \underset{H_2O}{\overset{HO^-}{\rightleftharpoons}} R\text{—}\ddot{\underset{..}{S}}{:}^- \xrightarrow{Br\text{—}Br} R\text{—}S\text{—}Br + Br^- \xrightarrow{R\text{—}\ddot{\underset{..}{S}}{:}^-} R\text{—}\ddot{\underset{..}{S}}\text{—}\ddot{\underset{..}{S}}\text{—}R + Br^-$$

- A thiolate ion attacks the electrophilic bromine of Br_2.
- A second thiolate ion attacks the sulfur and eliminates Br^-.

Because thiols can be oxidized to disulfides, disulfides can be reduced to thiols.

$$\underset{\text{a disulfide}}{RS\text{—}SR} \xrightarrow{\text{reduction}} \underset{\text{a thiol}}{2\ R\text{—}SH}$$

Disulfides are reduced to thiols.

The amino acid cysteine contains a thiol group, so two cysteine molecules can be oxidized to a disulfide. The disulfide is called cystine.

$$\underset{\text{cysteine}}{2\ HSCH_2CH(\overset{+}{N}H_3)C(=O)O^-} \xrightarrow{\text{mild oxidation}} \underset{\text{cystine}}{{}^-OC(=O)CH(\overset{+}{N}H_3)CH_2S\text{—}SCH_2CH(\overset{+}{N}H_3)C(=O)O^-}$$

Thiols are oxidized to disulfides.

Two cysteines in a protein can be oxidized to a disulfide, creating a bond known as a **disulfide bridge.** Disulfide bridges are the only covalent bonds that are found between nonadjacent amino acids in peptides and proteins. They contribute to the overall shape of a protein by linking cysteines found in different parts of the peptide backbone, as shown in Figure 17.7.

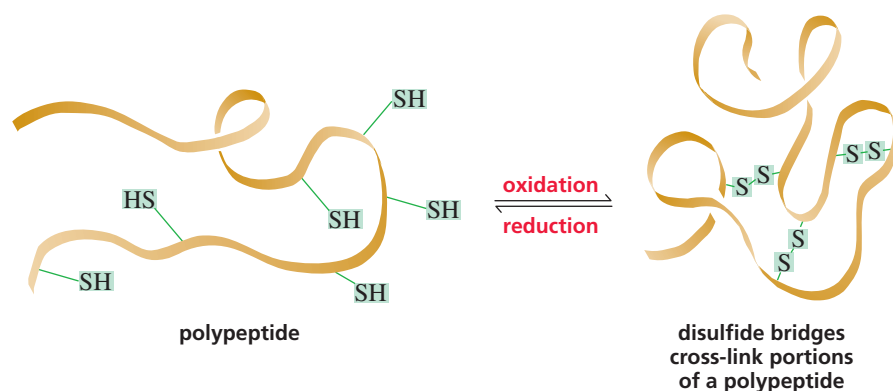
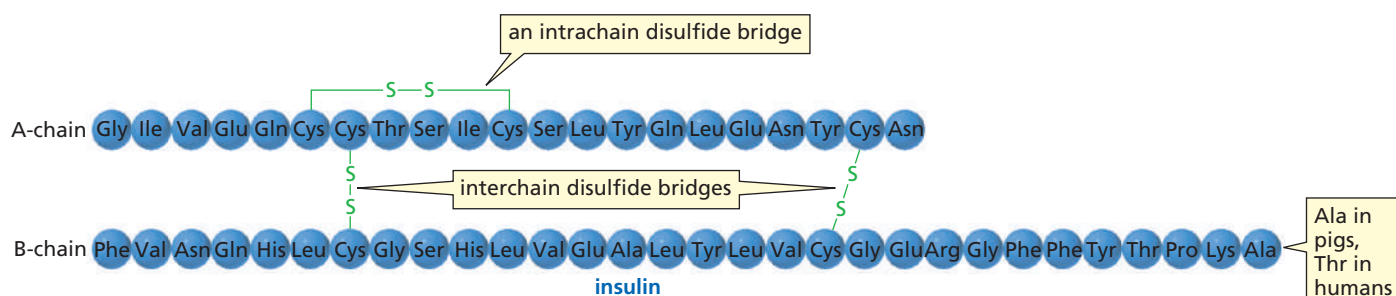
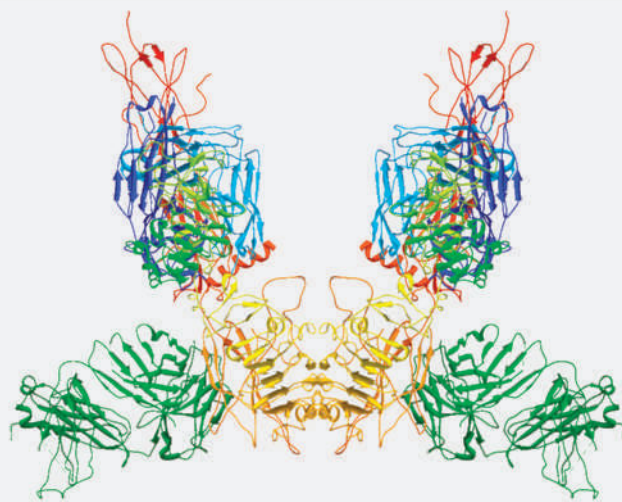



Figure 17.7
Disulfide bridges cross-link portions of a polypeptide.

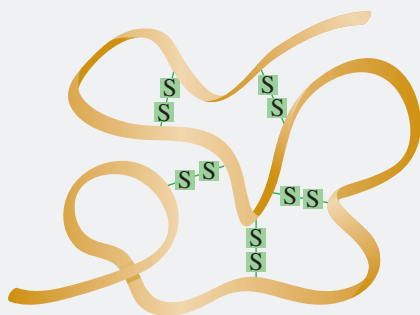
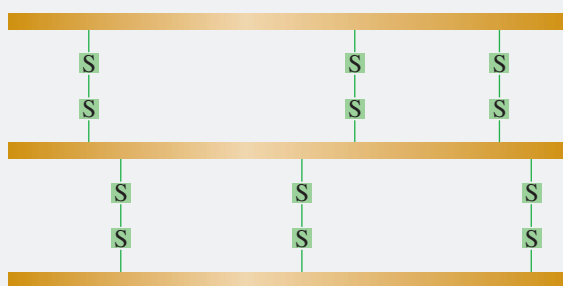
The hormone insulin, synthesized in the pancreas by cells known as the islets of Langerhans, maintains the proper level of glucose in the blood. Insulin is a polypeptide with two peptide chains; one contains 21 amino acids and the other 30 amino acids. The two chains are connected to each other by two **interchain disulfide bridges** (between two chains). Insulin also has an **intrachain disulfide bridge** (within a chain).

Diabetes

Diabetes is the third leading cause of death (heart disease and cancer are the first and second) in the United States. It is caused either by insufficient secretion of insulin (type 1 diabetes) or its inability to stimulate its target cells (type 2 diabetes). Injections of insulin can control some of the symptoms associated with diabetes.

Until genetic engineering techniques became available (Section 21.13), pigs were the primary source of insulin for people with diabetes. The insulin was effective, but there were concerns about whether enough could be obtained over the long term for the growing population of people with diabetes. In addition, the C-terminal amino acid of the B-chain is alanine in pig insulin and threonine in human insulin, which caused some people to have allergic reactions. Now, however, mass quantities of synthetic insulin, chemically identical to human insulin, are produced from genetically modified host cells.

Insulin binds to the insulin receptor on the surface of cells, signalling the cell to transport glucose from the blood into the cell.

Hair: Straight or Curly?

Hair is made up of a protein called keratin that contains an unusually large number of cysteines (about 8% of the amino acids compared to an average of 2.8% for other proteins). These cysteines furnish keratin with many disulfide bridges that preserve its three-dimensional structure.

People can alter the structure of their hair (if they think it is either too straight or too curly) by changing the location of these disulfide bridges. This can be accomplished by first applying a reducing agent to the hair to reduce all the disulfide bridges in the protein strands. Then, after rearranging the hair into the desired shape (using curlers to curl it or combing it straight to uncurl it), an oxidizing agent is applied to form new disulfide bridges. The new disulfide bridges hold the hair in its new shape. When this treatment is applied to straight hair, it is called a "permanent." When it is applied to curly hair, it is called "hair straightening."

PROBLEM 20

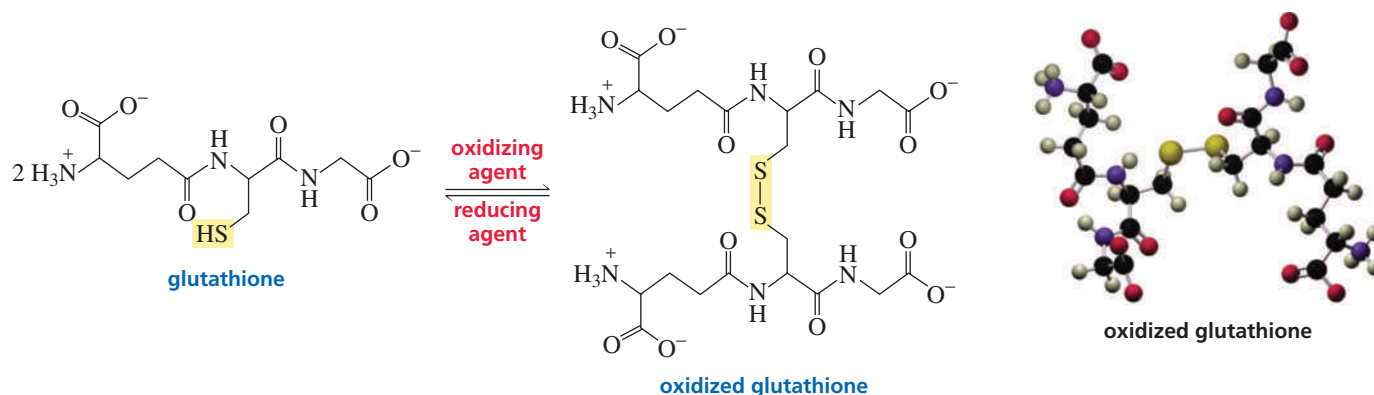
Glutathione is a tripeptide whose function is to destroy harmful oxidizing agents in the body. Oxidizing agents are thought to be responsible for some of the effects of aging and to play a causative role in cancer. Glutathione removes oxidizing agents by reducing them. In the process, glutathione is oxidized, resulting in the formation of a disulfide bond between two glutathione molecules. An enzyme subsequently reduces the disulfide bond, returning glutathione to its original condition so that it can react with another oxidizing agent.

glutathione

oxidizing agent

reducing agent

oxidized glutathione

oxidized glutathione

a. What amino acids make up glutathione?

b. What is unusual about glutathione's structure? (If you cannot answer this question, draw the structure you would expect for the tripeptide, and compare your structure with the actual structure.)

17.9 AN INTRODUCTION TO PROTEIN STRUCTURE

Proteins are described by four levels of structure, called primary, secondary, tertiary, and quaternary.

- The **primary structure** of a protein is the sequence of the amino acids in the chain and the location of all the disulfide bridges.
- **Secondary structures** are regular conformations assumed by segments of the protein's backbone when it folds.
- The **tertiary structure** is the three-dimensional structure of the entire protein.
- If a protein has more than one polypeptide chain, it also has a quaternary structure. The **quaternary structure** is the way the individual polypeptide chains are arranged with respect to one another.

Primary Structure and Taxonomic Relationship

When scientists examine the primary structures of proteins that carry out the same function in different organisms, they can correlate the number of amino acid differences in the proteins to the closeness of the taxonomic relationship between the species. For example, cytochrome *c*, a protein that transfers electrons in biological oxidations, has about 100 amino acids. Yeast cytochrome *c* differs by 48 amino acids from horse cytochrome *c*, whereas duck cytochrome *c* differs by only 2 amino acids from chicken cytochrome *c*. Ducks and chickens, therefore, have a much closer taxonomic relationship than do horses and yeast. The cytochrome *c* in chickens and turkeys have identical primary structures. Human cytochrome *c* and chimpanzee cytochrome *c* are also identical and differ by 1 amino acid from the cytochrome *c* of the rhesus monkey.

17.10 HOW TO DETERMINE THE PRIMARY STRUCTURE OF A POLYPEPTIDE OR A PROTEIN

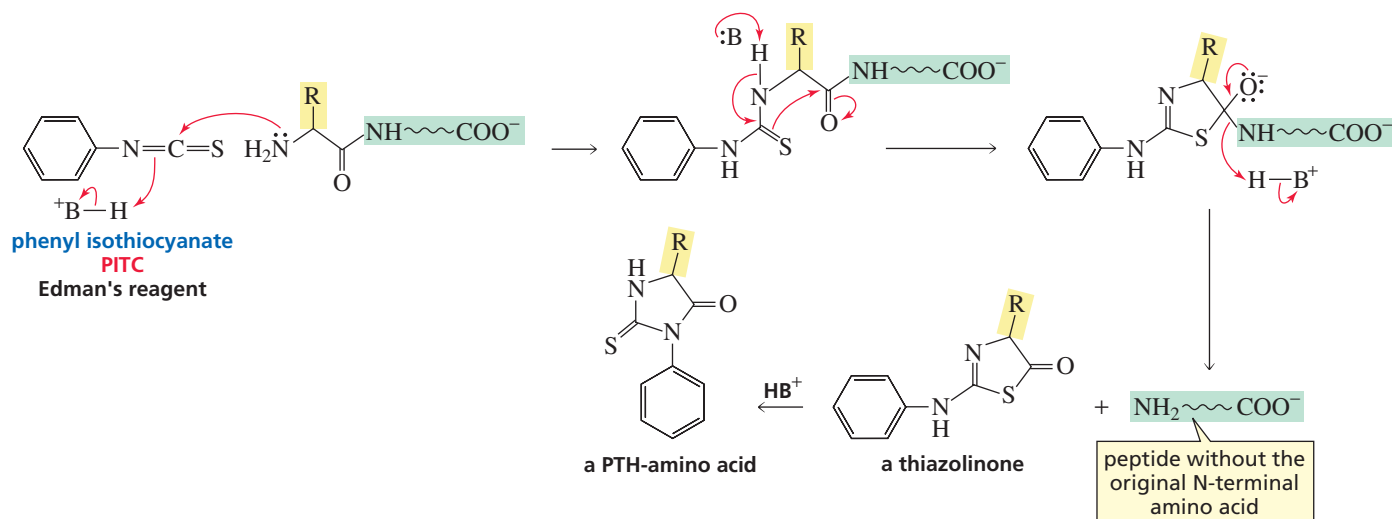
Determining the N-Terminal Amino Acid

One of the most widely used methods to identify the N-terminal amino acid of a polypeptide is to treat the polypeptide with phenyl isothiocyanate (PITC), more commonly known as **Edman's reagent.** Edman's reagent reacts with the N-terminal amino group, and the resulting thiazolinone derivative is cleaved from the polypeptide under mildly acidic conditions, leaving behind a polypeptide with one less amino acid. The thiazolinone rearranges in dilute acid to a more stable phenylthiohydantoin (PTH).

phenyl isothiocyanate
PITC
Edman's reagent

a PTH-amino acid

a thiazolinone

peptide without the original N-terminal amino acid

Because each amino acid has a different side chain (R), each amino acid forms a different PTH-amino acid. The particular PTH-amino acid can be identified by chromatography using known standards.

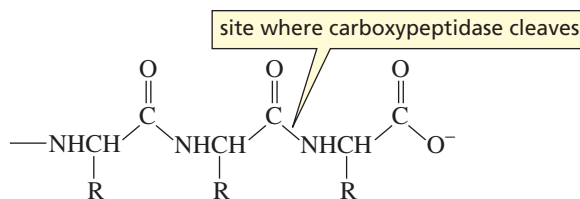
An automated instrument known as a *sequencer* allows about 50 successive Edman degradations of a polypeptide to be performed (more advanced instruments allow 100). The entire primary structure cannot be determined in this way, however, because side products accumulate that interfere with the results.

PROBLEM 21♦

In determining the primary structure of insulin, what would lead you to conclude that insulin has more than one polypeptide chain?

Determining the C-Terminal Amino Acid

The C-terminal amino acid of a polypeptide can be identified using a carboxypeptidase, an enzyme that catalyzes the hydrolysis of the C-terminal peptide bond, thereby cleaving off the C-terminal amino acid. Carboxypeptidase A cleaves off the C-terminal amino acid, as long as it is *not* arginine or lysine. On the other hand, carboxypeptidase B cleaves off the C-terminal amino acid, *only* if it is arginine or lysine. Carboxypeptidases are **exopeptidases,** enzymes that catalyze the hydrolysis of a peptide bond at the end of a peptide chain.

site where carboxypeptidase cleaves

Carboxypeptidases cannot be used to determine the amino acid sequence at the C-terminal end of a peptide by cleaving off the C-terminal amino acids sequentially, because peptide bonds hydrolyze at different rates. For example, if the C-terminal amino acid hydrolyzed slowly and the next one hydrolyzed rapidly, then it would appear that they were being cleaved off at about the same rate.

Partial Hydrolysis

Once the N-terminal and C-terminal amino acids have been identified, a sample of the polypeptide is hydrolyzed under conditions that hydrolyze only some of the peptide bonds—a procedure known as **partial hydrolysis.** The resulting fragments are separated, and the amino acid composition of each can be determined using electrophoresis or thin-layer chromatography. The process can be repeated and the sequence of the

original protein can then be deduced by lining up the peptides and looking for regions of overlap. (The N-terminal and C-terminal amino acids of each fragment can also be identified, if needed.)

PROBLEM-SOLVING STRATEGY

Sequencing an Oligopeptide

When a nonapeptide undergoes partial hydrolysis, it forms dipeptides, a tripeptide, and two tetrapeptides whose amino acid compositions are shown. Reaction of the intact nonapeptide with Edman's reagent releases PTH-Leu. What is the sequence of the nonapeptide?

1. Pro, Ser
2. Gly, Glu
3. Met, Ala, Leu
4. Gly, Ala
5. Glu, Ser, Val, Pro
6. Glu, Pro, Gly, Pro
7. Met, Leu
8. His, Val

- Because we know that the N-terminal amino acid is Leu, we need to look for a fragment that contains Leu. Fragment **7** tells us that Met is next to Leu, and fragment **3** tells us that Ala is next to Met.
- Now we look for another fragment that contains Ala. Fragment **4** contains Ala and tells us that Gly is next to Ala.
- From fragment **2**, we know that Glu comes next; Glu is in both fragments **5** and **6**.
- Fragment **5** has three amino acids we have yet to place in the growing peptide (Ser, Val, Pro), but fragment **6** has only one, so we know from fragment **6** that Pro is the next amino acid.
- Fragment **1** indicates that the next amino acid is Ser, so we can now use fragment **5**. Fragment **5** indicates that the next amino acid is Val, and fragment **8** tells us that His is the last (C-terminal) amino acid.
- Thus, the amino acid sequence of the nonapeptide is Leu-Met-Ala-Gly-Glu-Pro-Ser-Val-His

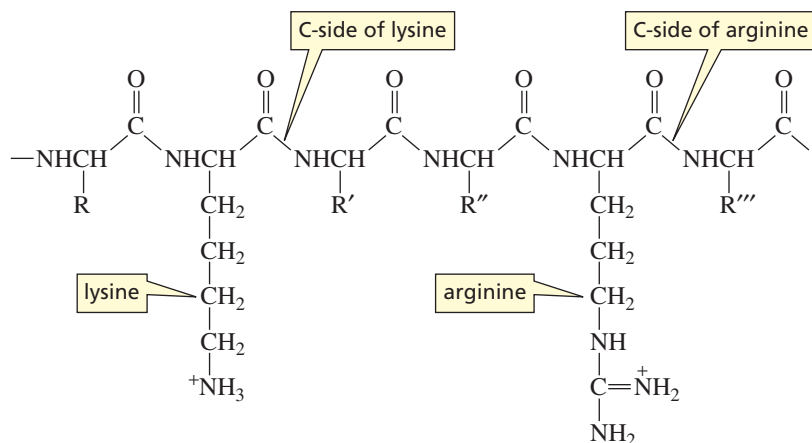
Now use the strategy you have just learned to solve Problem 22.

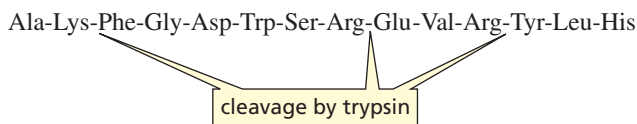
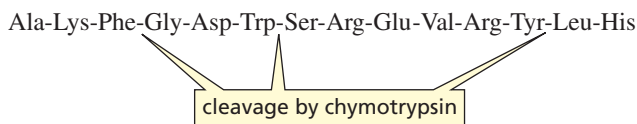
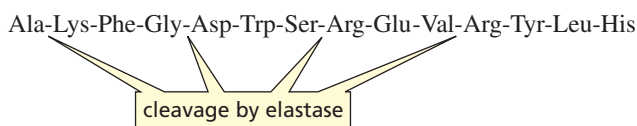
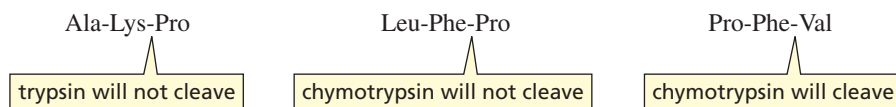
PROBLEM 22♦

A decapeptide undergoes partial hydrolysis to give peptides whose amino acid compositions are shown. Reaction of the intact decapeptide with Edman's reagent releases PTH-Gly. What is the sequence of the decapeptide?

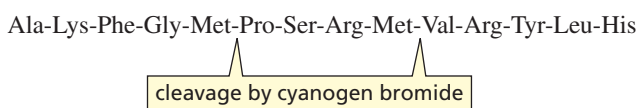
1. Ala, Trp
2. Val, Pro, Asp
3. Pro, Val
4. Ala, Glu
5. Trp, Ala, Arg
6. Arg, Gly
7. Glu, Ala, Leu
8. Met, Pro, Leu, Glu

Hydrolysis Using Endopeptidases

A polypeptide can also be partially hydrolyzed using **endopeptidases**—enzymes that catalyze the hydrolysis of a peptide bond that is *not* at the end of a peptide chain. Trypsin, for example, catalyzes the hydrolysis of the peptide bond on the C-side of (meaning, on the right of) positively charged side chains (arginine or lysine). These enzymes belong to the group of enzymes known as **digestive enzymes.**

trypsin
(see the legend to Figure 17.10)

Thus, trypsin will catalyze the hydrolysis of three peptide bonds in the following polypeptide, creating a hexapeptide, a dipeptide, and two tripeptides.

Chymotrypsin catalyzes the hydrolysis of the peptide bond on the C-side of amino acids that contain aromatic six-membered rings (Phe, Tyr, Trp).

Elastase catalyzes the hydrolysis of peptide bonds on the C-side of the four smallest amino acids (Gly, Ala, Ser, and Val). Chymotrypsin and elastase are much less specific than trypsin. (An explanation for the specificity of these enzymes is given in Section 18.3.)

None of the exopeptidases or endopeptidases that we have discussed will catalyze the hydrolysis of a peptide bond if proline is at the hydrolysis site. These enzymes recognize the appropriate hydrolysis site by its shape, and the cyclic structure of proline causes the hydrolysis site to have an unrecognizable three-dimensional shape.

Cyanogen bromide (BrC≡N) hydrolyzes the peptide bond on the C-side of methionine. Cyanogen bromide is more specific than the endopeptidases about which peptide bonds it cleaves, so it provides more reliable information about the primary structure. Because cyanogen bromide is not a protein, it does not recognize the substrate by its shape. As a result, it will still cleave the peptide bond if proline is at the hydrolysis site.

Ala-Lys-Phe-Gly-Met-Pro-Ser-Arg-Met-Val-Arg-Tyr-Leu-His

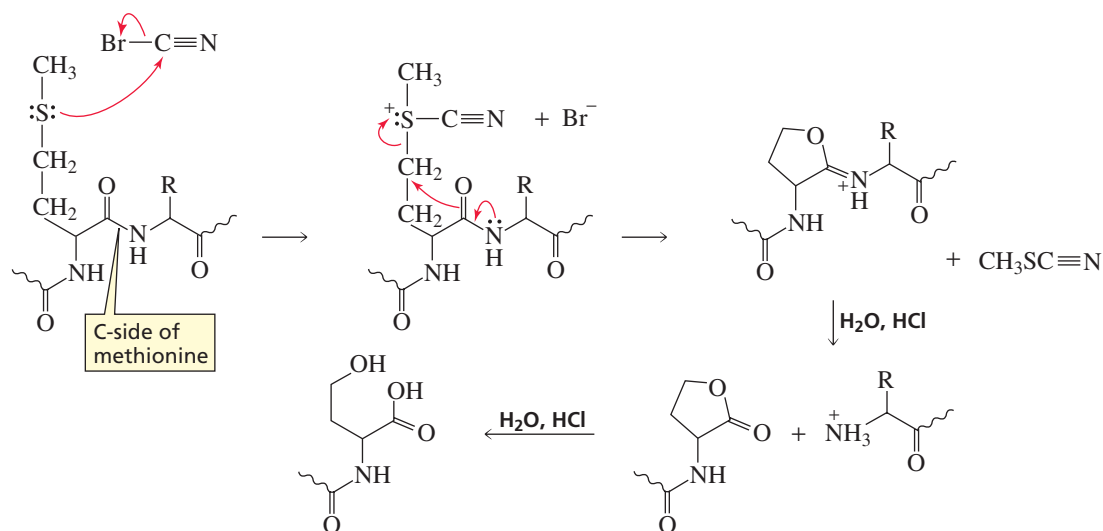
cleavage by cyanogen bromide

MECHANISM FOR THE CLEAVAGE OF A PEPTIDE BOND BY CYANOGEN BROMIDE

C-side of methionine

$+ Br^-$

$+ CH_3SC{\equiv}N$

H_2O, HCl

H_2O, HCl

- The nucleophilic sulfur of methionine attacks the carbon of cyanogen bromide and displaces a bromide ion.
- Nucleophilic attack by oxygen on the methylene group, resulting in departure of the weakly basic leaving group, forms a five-membered ring.
- Acid-catalyzed hydrolysis of the imine cleaves the protein (Section 12.8).
- Further hydrolysis causes the cyclic ester to open to a carboxyl group and an alcohol group (Section 11.9).

The last step in determining the primary structure of a protein is to figure out the location of any disulfide bonds. How this is done is described in Problem 45.

PROBLEM 23

Why does cyanogen bromide not cleave on the C-side of cysteine?

PROBLEM 24♦

Indicate the peptides that would result from cleavage by the indicated reagent:

a. His-Lys-Leu-Val-Glu-Pro-Arg-Ala-Gly-Ala by trypsin
b. Leu-Gly-Ser-Met-Phe-Pro-Tyr-Gly-Val by chymotrypsin

PROBLEM 25 Solved

Determine the amino acid sequence of a polypeptide from the following data:

Acid-catalyzed hydrolysis gives Ala, Arg, His, 2 Lys, Leu, 2 Met, Pro, 2 Ser, Thr, and Val.

Carboxypeptidase A releases Val.

Edman's reagent releases PTH-Leu.

Treatment with cyanogen bromide gives three peptides with the following amino acid compositions:

1. His, Lys, Met, Pro, Ser **2.** Thr, Val **3.** Ala, Arg, Leu, Lys, Met, Ser

Trypsin-catalyzed hydrolysis gives three peptides and a single amino acid:

1. Arg, Leu, Ser **3.** Lys
2. Met, Pro, Ser, Thr, Val **4.** Ala, His, Lys, Met

Solution Acid-catalyzed hydrolysis shows that the polypeptide has 13 amino acids. The N-terminal amino acid is Leu (revealed by Edman's reagent), and the C-terminal amino acid is Val (revealed by carboxypeptidase A).

Leu ____ ____ ____ ____ ____ ____ ____ ____ ____ ____ ____ Val

- Because cyanogen bromide cleaves on the C-side of Met, any peptide containing Met must have Met as its C-terminal amino acid. Thus, the peptide that does not contain Met must be the C-terminal peptide, so we know that the 12th amino acid is Thr. We know that peptide **3** is the N-terminal peptide because it contains Leu. Because peptide **3** is a hexapeptide, we know that the sixth amino acid in the polypeptide is Met. We also know that the 11th amino acid is Met because cyanogen bromide cleavage gave the dipeptide Thr, Val.

Ala, Arg, Lys, Ser His, Lys, Pro, Ser

Leu ____ ____ ____ ____ Met ____ ____ ____ ____ Met Thr Val

- Because trypsin cleaves on the C-side of Arg and Lys, any peptide containing Arg or Lys must have that amino acid as its C-terminal amino acid. Therefore, Arg is the C-terminal amino acid of peptide **1**, so we now know that the first three amino acids are Leu-Ser-Arg. We also know that the next two are Lys-Ala because if they were Ala-Lys, then trypsin cleavage would give an Ala, Lys dipeptide. The trypsin data also identify the positions of His and Lys.

Pro, Ser

Leu Ser Arg Lys Ala Met His Lys ____ ____ Met Thr Val

- Finally, because trypsin successfully cleaves on the C-side of Lys, Pro cannot be adjacent to Lys. Thus, the amino acid sequence of the polypeptide is

Leu Ser Arg Lys Ala Met His Lys Ser Pro Met Thr Val

PROBLEM 26

Determine the primary structure of an octapeptide from the following data:

Acid-catalyzed hydrolysis gives 2 Arg, Leu, Lys, Met, Phe, Ser, and Tyr.

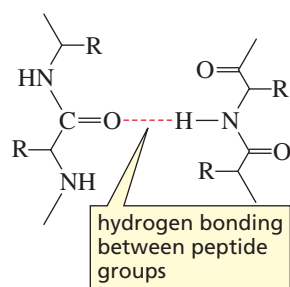
Carboxypeptidase A releases Ser.

Edman's reagent releases Leu.

Treatment with cyanogen bromide forms two peptides with the following amino acid compositions:

1. Arg, Phe, Ser **2.** Arg, Leu, Lys, Met, Tyr

Trypsin-catalyzed hydrolysis forms the following two amino acids and two peptides:

1. Arg **2.** Ser **3.** Arg, Met, Phe **4.** Leu, Lys, Tyr

17.11 SECONDARY STRUCTURE

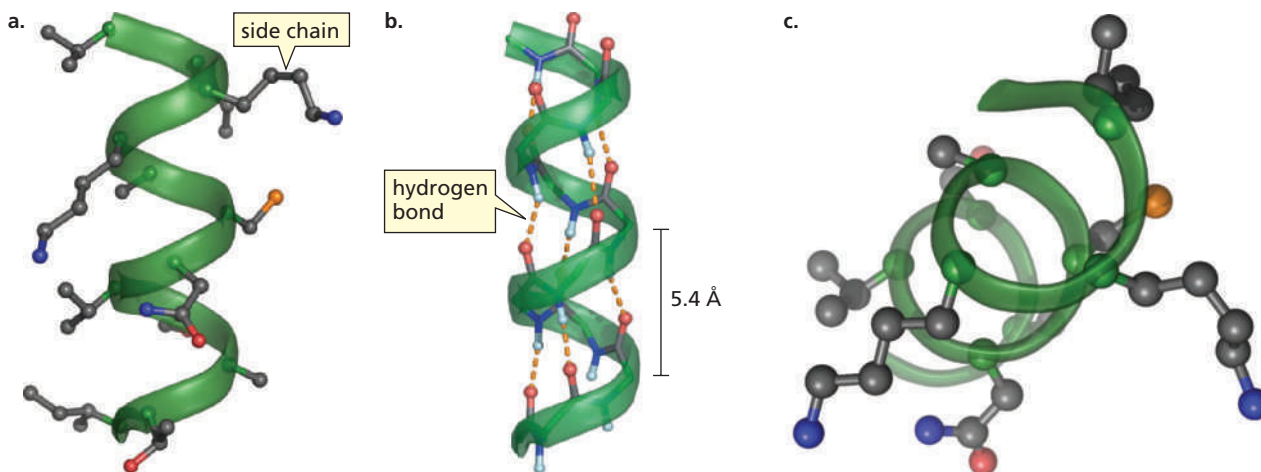
Secondary structure describes the repetitive conformations assumed by segments of the backbone chain of a peptide or protein. In other words, the secondary structure describes how segments of the backbone fold. Three factors determine the secondary structure of a segment of protein:

hydrogen bonding between peptide groups

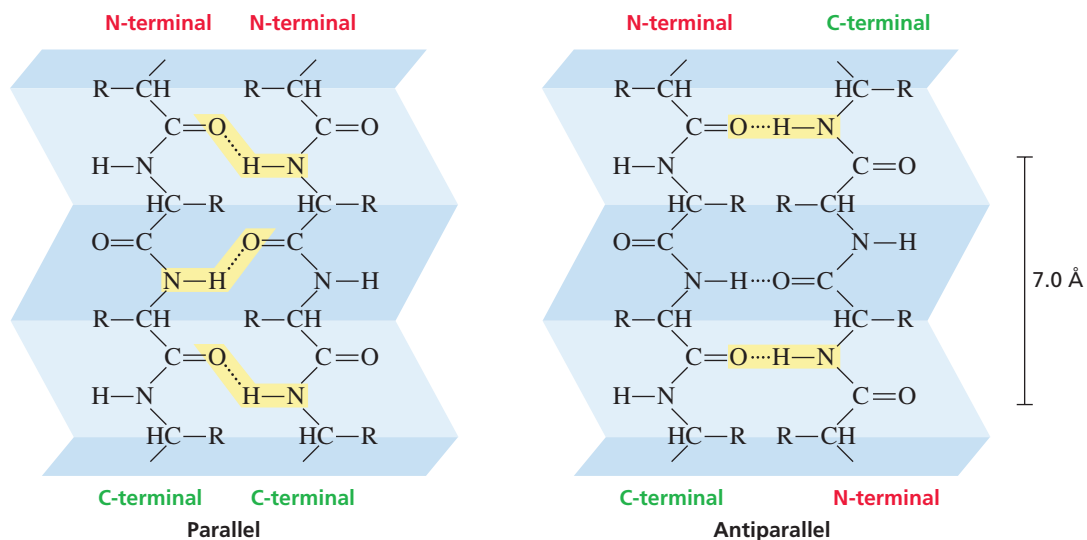
- the regional planarity about each peptide bond (as a result of the partial double-bond character of the amide bond), which limits the possible conformations of the peptide chain (Section 17.8)
- minimizing energy by maximizing the number of peptide groups that engage in hydrogen bonding (that is, that form a hydrogen bond between the carbonyl oxygen of one amino acid and the amide hydrogen of another)
- the need for adequate separation between neighboring R groups to avoid steric strain and repulsion of like charges

α-Helix

One type of secondary structure is an **α-helix.** In an α-helix, the backbone of the polypeptide coils around the long axis of the protein molecule. The side chains (substituents) on the α-carbons of the amino acids protrude outward from the helix, thereby minimizing steric strain (Figure 17.8a). The helix is stabilized by hydrogen bonds—each hydrogen attached to an amide nitrogen is hydrogen bonded to a carbonyl oxygen of an amino acid four amino acids away (Figure 17.8b).

Because the amino acids have the L-configuration, the α-helix is a right-handed helix—that is, it rotates in a clockwise direction as it spirals down (Figure 17.8c).

▲ **Figure 17.8**
(a) A segment of a protein in an α-helix.
(b) The helix is stabilized by hydrogen bonding between peptide groups.
(c) Looking down the longitudinal axis of an α-helix.

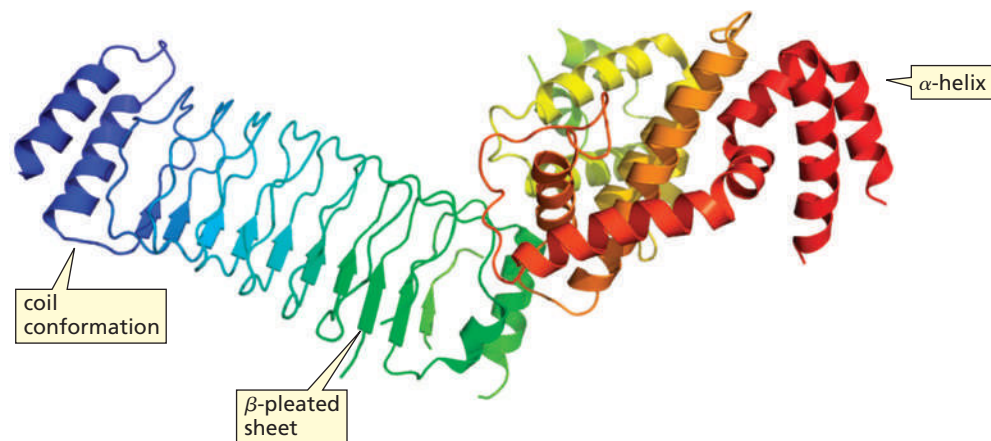
β-Pleated Sheet

The second type of secondary structure is a **β-pleated sheet.** In a β-pleated sheet, the polypeptide backbone is extended in a zigzag structure resembling a series of pleats. The hydrogen bonding in a β-pleated sheet occurs between neighboring peptide chains, and these chains can run in the same direction or in opposite directions—called a **parallel β-pleated sheet** and an **antiparallel β-pleated sheet** (Figure 17.9).

▲ **Figure 17.9**
Segments of a parallel β-pleated sheet and an antiparallel β-pleated sheet drawn to illustrate their pleated character.

Because the substituents (R) on the α-carbons of the amino acids on adjacent chains are close to each other, the substituents must be small if the chains are to nestle closely enough together to maximize hydrogen-bonding interactions. Silk, for example, contains a large proportion of relatively small amino acids (glycine and alanine) and, therefore, has large segments of β-pleated sheet.

Wool and the fibrous protein of muscle have secondary structures that are almost all α-helices. Consequently, these proteins can be stretched. In contrast, proteins with secondary structures that are predominantly β-pleated sheets, such as silk and spider webs, cannot be stretched because a β-pleated sheet is almost fully extended already.

Coil Conformation

Generally, less than half of the protein's backbone is arranged in a defined secondary structure—an α-helix or a β-pleated sheet (Figure 17.10). Most of the rest of the protein, though highly ordered, is nonrepetitive and, therefore, difficult to describe. Many of these ordered polypeptide fragments are said to be in **coil** or **loop conformations.**

◀ **Figure 17.10**
The backbone structure of an enzyme called ligase (Section 21.5): a β-pleated sheet is indicated by a flat arrow pointing in the N → C direction, an α-helix by a flat helical ribbon, and a coil or loop conformation by a thin tube.

17.12 TERTIARY STRUCTURE

The *tertiary structure* of a protein is the three-dimensional arrangement of all the atoms in the protein (Figure 17.11). Proteins fold spontaneously in solution to maximize their stability. Every time there is a stabilizing interaction between two atoms, free energy is released. The more free energy released (the more negative the ΔG°), the more stable the protein. Consequently, a protein tends to fold in a way that maximizes the number of stabilizing interactions.

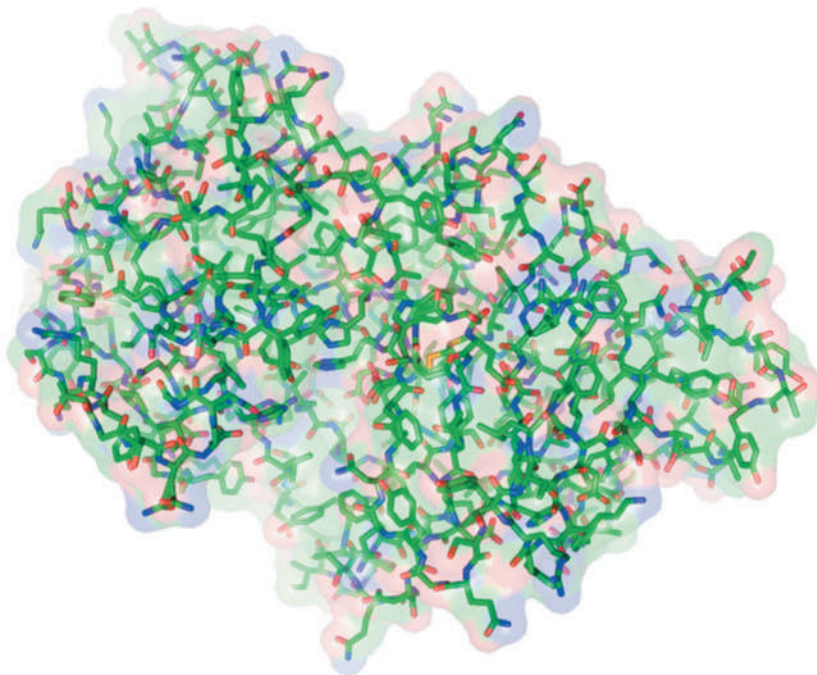



Figure 17.11
The three-dimensional structure of thermolysin (an endopeptidase).

The stabilizing interactions in a protein include disulfide bonds, hydrogen bonds, electrostatic attractions (attractions between opposite charges), and hydrophobic (van der Waals) interactions. Stabilizing interactions can occur between peptide groups (atoms in the backbone of the protein), between side-chain groups (α-substituents), and between peptide and side-chain groups (Figure 17.12). Because the side-chain groups help determine how a protein folds, the tertiary structure of a protein is greatly affected by its primary structure.

Disulfide bonds are the only covalent bonds that can form when a protein folds. The other bonding interactions that occur in folding are much weaker, but because there are so many of them, they are important in determining how a protein folds.

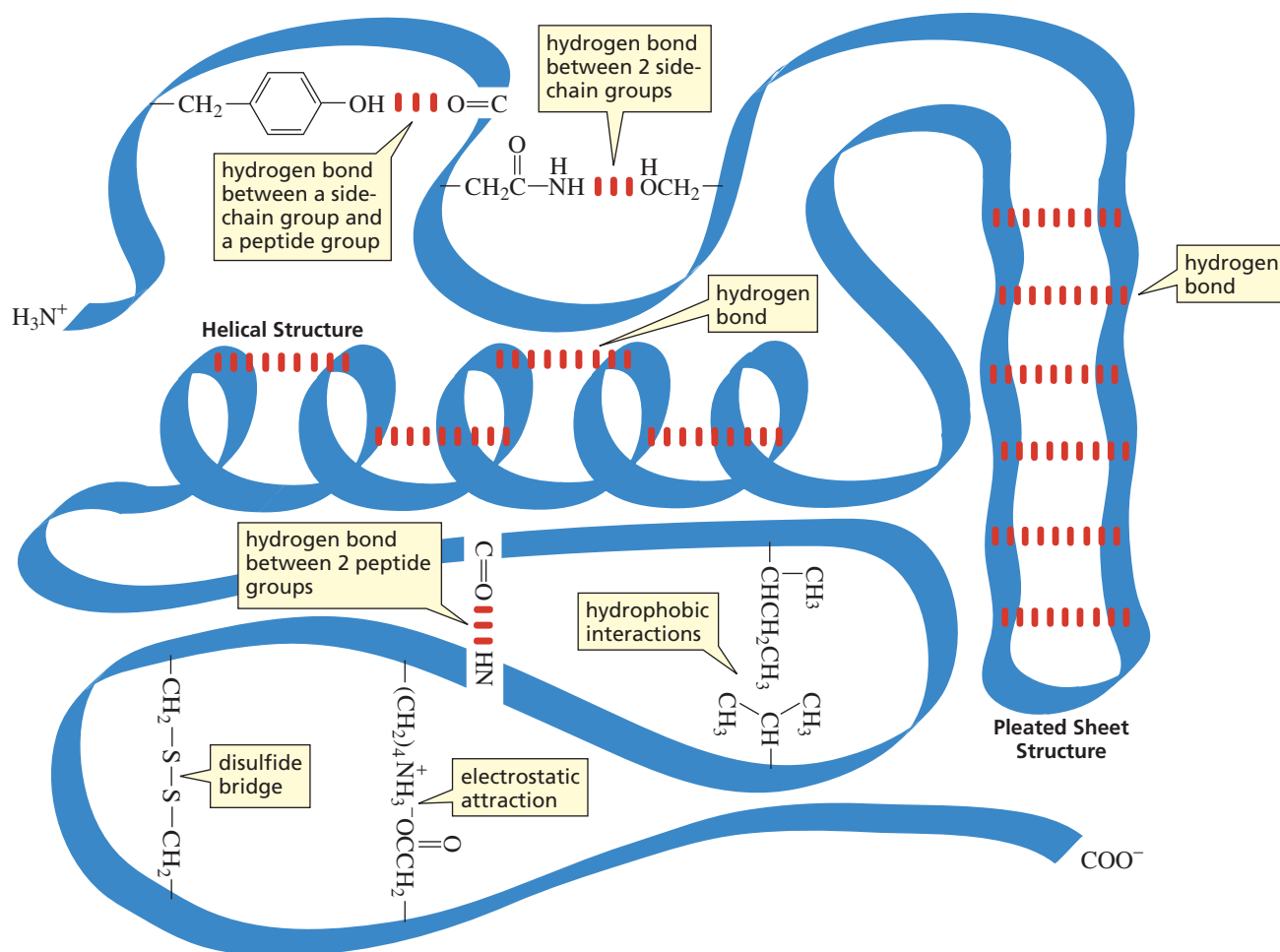
Most proteins exist in aqueous environments, so they tend to fold in a way that exposes the maximum number of polar groups to the surrounding water and buries the nonpolar groups in the protein's interior, away from water.

The **hydrophobic interactions** between nonpolar groups in the protein increase its stability by increasing the entropy of water molecules. Groups of water molecules that surround nonpolar groups are highly structured. When two nonpolar groups come together, the surface area in contact with water diminishes, decreasing the amount of structured water. Decreasing structure increases entropy, which in turn decreases the free energy, thereby increasing the stability of the protein. (Recall that $\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$.)

The precise mechanism by which proteins fold is still an unanswered question. Protein misfolding has been linked to numerous diseases such as Alzheimer's disease and Huntington's disease.

PROBLEM 27

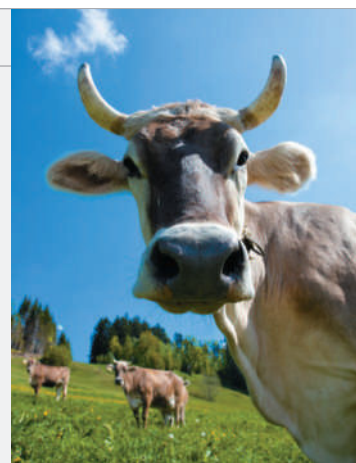
How would a protein that resides in the nonpolar interior of a membrane fold compared with the water-soluble protein just discussed?

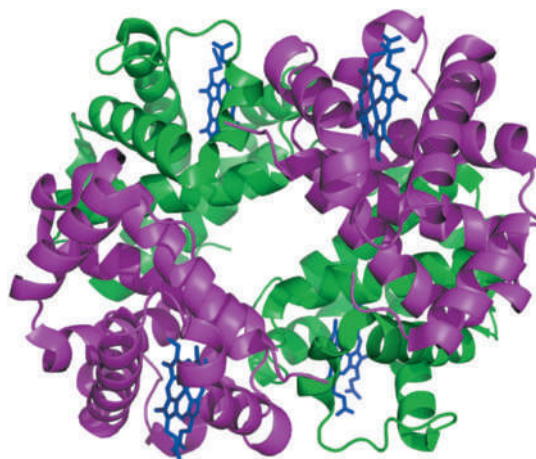
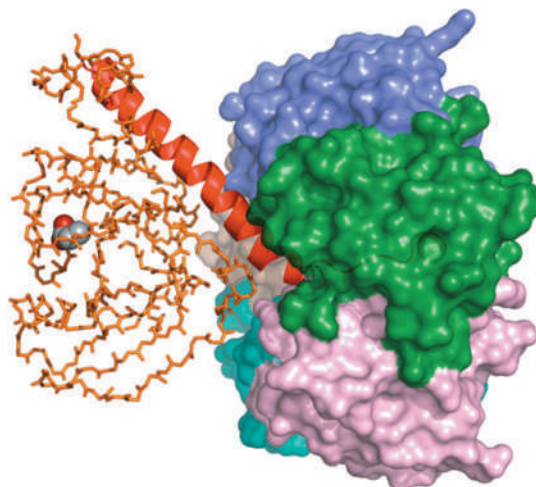
hydrogen bond between 2 side-chain groups
hydrogen bond between a side-chain group and a peptide group
hydrogen bond
Helical Structure
hydrogen bond
Pleated Sheet Structure
hydrogen bond between 2 peptide groups
hydrophobic interactions
disulfide bridge
electrostatic attraction
H_3N^+
COO^-

▲ **Figure 17.12**
Stabilizing interactions responsible for the tertiary structure of a protein.

Diseases Caused by a Misfolded Protein

Bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, is unlike most other diseases because it is not caused by a microorganism. Instead, it caused by a misfolded protein in the brain called a prion. It is not yet known what causes the prion to become misfolded. The misfolded prion causes cells to deteriorate until the brain has a sponge-like appearance. The deterioration causes the loss of mental function, which makes cows with the disease act strangely (hence the name *mad cow disease*). It is not curable and it is fatal, but it is not contagious. It takes several years from the time of first exposure until the first signs of the disease appear, but then it progresses quickly.

There are other diseases caused by misfolded prions that have similar symptoms. Kuru—transmitted through cannibalism—has been found to occur in the Fore people of Papua New Guinea (*kuru* means "trembling"). Scrapie affects sheep and goats. This disease got its name from the tendency of sheep to scrape off their wool on fences as they lean on them in an attempt to stay upright. It is thought that mad cow disease, first reported in the U.K. in 1985, was caused by cows eating bone meal made from scrapie-infected sheep.

The human form of the disease is called Creutzfeldt–Jakob disease (CJD), which is rare and apparently arises spontaneously. The average age of onset of CJD is 64. In 1994, however, several cases of a new variant of the disease (vCJD) appeared in young adults in the U.K. To date, 200 cases have been reported. This new variant is caused by ingesting meat products of an animal infected with the disease.

17.13 QUATERNARY STRUCTURE

Some proteins have more than one polypeptide chain. The individual chains are called **subunits.** A protein with a single subunit is called a *monomer;* one with two subunits is called a *dimer;* one with three subunits is called a *trimer;* and one with four subunits is called a *tetramer*. The quaternary structure of a protein describes the way the subunits are arranged with respect to each other (Figures 17.13 and 17.14).

▲ **Figure 17.13**
The quaternary structure of hemoglobin. It is a tetramer; it has two different kinds of subunits and each hemoglobin molecule has two of each kind. The porphyrin rings that bind O_2 and CO_2 are blue.

▲ **Figure 17.14**
Escherichia coli heat-labile enterotoxin has seven subunits. Five of them (blue, green, purple, etc.) attach to a cell membrane. The red helical spike delivers the catalytic subunit (orange) into the cell. This toxin is responsible for what is known as traveler's diarrhea.

The subunits of a protein are held together by the same kinds of interactions that hold the individual protein chains in a particular three-dimensional conformation—namely, hydrophobic interactions, hydrogen bonding, and electrostatic attractions.

PROBLEM 28

a. Which would have the greatest percentage of polar amino acids: a spherical protein, a cigar-shaped protein, or a subunit of a hexamer?

b. Which would have the smallest percentage of polar amino acids?

17.14 PROTEIN DENATURATION

Destroying the highly organized tertiary structure of a protein is called **denaturation.** Anything that breaks the interactions maintaining the three-dimensional shape of the protein will cause the protein to denature (unfold). Because these interactions are weak, proteins are easily denatured. The following are some of the ways that proteins can be denatured:

- Changing the pH denatures proteins because it changes the charges on many of the side chains. This disrupts electrostatic attractions and hydrogen bonds.
- Certain reagents such as urea denature proteins by forming hydrogen bonds to protein groups that are stronger than the hydrogen bonds formed between the groups.
- Organic solvents denature proteins by associating with the nonpolar groups of the protein, thereby disrupting the normal hydrophobic interactions.
- Proteins can also be denatured by heat or by agitation. Both disrupt the attractive forces. A well-known example is the change that occurs to the white of an egg when it is heated or whipped.

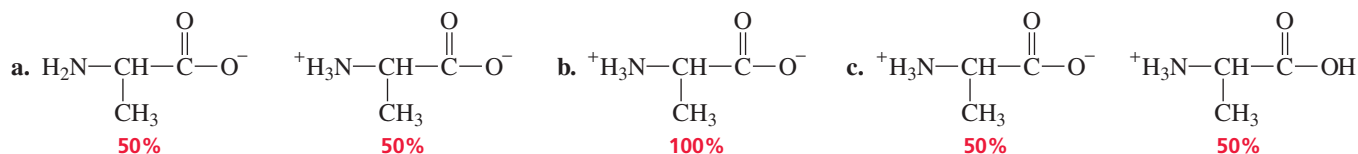
SOME IMPORTANT THINGS TO REMEMBER

- **Peptides** and **proteins** are polymers of **amino acids** linked together by **peptide** (amide) bonds.
- The **amino acids** differ only in the substituent attached to the α-carbon.
- Almost all amino acids found in nature have the L-configuration.
- The carboxyl groups of the amino acids have pK_a values of ~2, and the protonated amino groups have pK_a values of ~9. At physiological pH (7.4), an amino acid exists as a **zwitterion.**
- The **isoelectric point** (pI) of an amino acid is the pH at which the amino acid has no net charge.
- A mixture of amino acids can be separated based on their pI values by **electrophoresis** or based on their polarities by **paper chromatography** or **thin-layer chromatography.**
- Separation can also be done by **ion-exchange chromatography** employing a **cation-exchange resin.** An **amino acid analyzer** is an instrument that automates ion-exchange chromatography.
- Amino acids can be synthesized by a reductive amination, a *N*-phthalimidomalonic ester synthesis, or a Strecker synthesis.
- A racemic mixture of amino acids can be separated using an enzyme-catalyzed reaction that can distinguish enantiomers or derivatives of the enantiomers.
- Rotation about a peptide bond is restricted because of its partial double-bond character.
- Two cysteine side chains can be oxidized to a **disulfide bridge,** the only kind of covalent bond that is found between nonadjacent amino acids.
- By convention, peptides and proteins are written with the free amino group (of the **N-terminal amino acid**) on the left and the free carboxyl group (of the **C-terminal amino acid**) on the right.
- The **primary structure** of a protein is the sequence of its amino acids and the location of all its disulfide bridges.
- The N-terminal amino acid can be determined with **Edman's reagent.** The C-terminal amino acid can be identified with a carboxypeptidase.
- An **exopeptidase** catalyzes the hydrolysis of a peptide bond at the end of a peptide chain. An **endopeptidase** catalyzes the hydrolysis of a peptide bond that is not at the end of a peptide chain.
- The **secondary structure** of a protein describes how local segments of the protein's backbone fold. An α**-helix** and a β**-pleated sheet** are two types of secondary structure.
- A protein folds so as to maximize the number of stabilizing interactions—namely, **disulfide bonds, hydrogen bonds, electrostatic attractions,** and **hydrophobic interactions.**
- The **tertiary structure** of a protein is the three-dimensional arrangement of all the atoms in the protein.
- The **quaternary structure** of a protein describes the way the peptide chains (subunits) of a protein with more than one peptide chain are arranged with respect to each other.

PROBLEMS

29. Draw the predominant form of the following amino acids at physiological pH (7.4):
a. alanine **b.** glutamic acid **c.** leucine

30. What is the pI of arginine?

31. Alanine has pK_a values of 2.34 and 9.60. At what pH will alanine exist in the indicated form?

32. Show the peptides that would result from cleavage by the indicated reagent:
a. Val-Arg-Gly-Met-Arg-Ala-Ser by carboxypeptidase A
b. Ser-Phe-Lys-Met-Pro-Ser-Ala-Asp by cyanogen bromide
c. Arg-Ser-Pro-Lys-Lys-Ser-Glu-Gly by trypsin

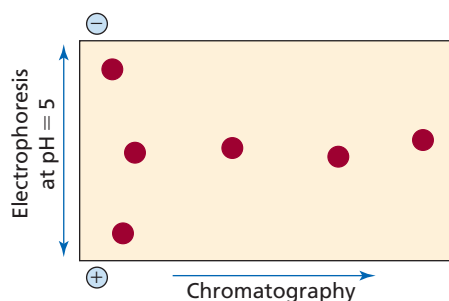
33. Which would have a higher percentage of negative charge at physiological pH (7.4): alanine with pI = 6.02 or asparagine with pI = 5.43?

34. Draw the form of glycine that predominates at the following pH values:
a. pH = 1.0 **b.** pH = 2.6 **c.** pH = 6.0 **d.** pH = 11.0

35. Cysteine has pK_a values of 1.92 and 10.46. Therefore, cysteine will exist predominantly as a zwitterion in an aqueous solution with pH > ____ and pH < ____.

36. A professor was preparing a manuscript for publication in which she reported that the pI of the tripeptide Lys-Lys-Lys was 10.6. One of her students pointed out that there must be an error in her calculations because the pK_a of the side-chain amino group of lysine is 10.8 and the pI of the tripeptide has to be greater than any of its individual pK_a values. Was the student correct?

37. **a.** Why is the pK_a of the glutamate side chain greater than the pK_a of the aspartate side chain?
b. Why is the pK_a of the arginine side chain greater than the pK_a of the lysine side chain?

38. A mixture of amino acids that do not separate sufficiently when a single technique is used can often be separated by two-dimensional chromatography. In this technique, the mixture of amino acids is applied to a piece of filter paper and separated by chromatographic techniques. The paper is then rotated 90°, and the amino acids are further separated by electrophoresis, producing a type of chromatogram called a *fingerprint*. Identify the spots in the fingerprint obtained from a mixture of Ser, Glu, Leu, His, Met, and Thr.

39. Determine the amino acid sequence of a polypeptide from the following data:

Complete hydrolysis of the peptide yields Arg, 2 Gly, Ile, 3 Leu, 2 Lys, 2 Met, 2 Phe, Pro, Ser, 2 Tyr, and Val.

Treatment with Edman's reagent releases PTH-Gly.

Carboxypeptidase A releases Phe.

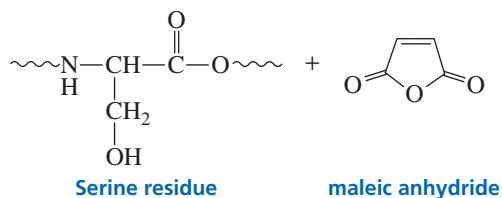
Treatment with cyanogen bromide yields the following three peptides:
1. Gly-Leu-Tyr-Phe-Lys-Ser-Met **2.** Gly-Leu-Tyr-Lys-Val-Ile-Arg-Met **3.** Leu-Pro-Phe

Treatment with trypsin yields the following four peptides:
1. Gly-Leu-Tyr-Phe-Lys
2. Ser-Met-Gly-Leu-Tyr-Lys
3. Val-Ile-Arg
4. Met-Leu-Pro-Phe

40. Which would be a more effective buffer at physiological pH, a solution of 0.3 M leuleuleuleuleuleucine or a solution of 0.8 M leucine?

41. Identify the location and type of charge on the hexapeptide Lys-Ser-Asp-Cys-His-Tyr at each of the following pH values:
a. pH = 1 **b.** pH = 5 **c.** pH = 7 **d.** pH = 12

42. Three peptides were obtained from a trypsin digestion of two different polypeptides. In each case, indicate the possible sequences from the given data and tell what further experiment should be carried out in order to determine the primary structure of the polypeptide.
a. **1.** Val-Gly-Asp-Lys **2.** Leu-Glu-Pro-Ala-Arg **3.** Ala-Leu-Gly-Asp
b. **1.** Val-Leu-Gly-Glu **2.** Ala-Glu-Pro-Arg **3.** Ala-Met-Gly-Lys

43. Draw the product obtained when a serine side chain in a polypeptide reacts with maleic anhydride.

~~~NH—CH(CH_2OH)—C(=O)—O~~~ + maleic anhydride

Serine residue maleic anhydride

44. After the polypeptide shown here was treated with maleic anhydride, it was hydrolyzed by trypsin. (After a polypeptide is treated with maleic anhydride, trypsin will cleave the polypeptide only on the C-side of arginine.)

Gly-Ala-Asp-Ala-Leu-Pro-Gly-Ile-Leu-Val-Arg-Asp-Val-Gly-Lys-Val-Glu-Val-Phe-Glu-Ala-Gly-
Arg-Ala-Glu-Phe-Lys-Glu-Pro-Arg-Leu-Val-Met-Lys-Val-Glu-Gly-Arg-Pro-Val-Gly-Ala-Gly-Leu-Trp

a. After a polypeptide is treated with maleic anhydride, why does trypsin no longer cleave it on the C-side of lysine?
b. How many fragments are obtained from the polypeptide?
c. In what order would the fragments be eluted from an anion-exchange column using a buffer of pH = 5?

45. The disulfide bridges of a polypeptide were reduced, yielding two polypeptides with the following primary structures:

Val-Met-Tyr-Ala-Cys-Ser-Phe-Ala-Glu-Ser
Ser-Cys-Phe-Lys-Cys-Trp-Lys-Tyr-Cys-Phe-Arg-Cys-Ser

Treatment of the original intact polypeptide with chymotrypsin yields the following peptides:
1. Ala, Glu, Ser
2. 2 Phe, 2 Cys, Ser
3. Tyr, Val, Met
4. Arg, Ser, Cys
5. Ser, Phe, 2 Cys, Lys, Ala, Trp
6. Tyr, Lys

Determine the positions of the disulfide bridges in the original polypeptide.

46. α-Amino acids can be prepared by treating an aldehyde with ammonia/trace acid, followed by hydrogen cyanide, followed by acid-catalyzed hydrolysis.
a. Draw the structures of the two intermediates formed in this reaction.
b. What amino acid is formed when the aldehyde that is used is 3-methylbutanal?
c. What aldehyde would be needed to prepare isoleucine?

47. Reaction of a polypeptide with carboxypeptidase A releases Met. The polypeptide undergoes partial hydrolysis to give the following peptides. What is the sequence of the polypeptide?
1. Ser, Lys, Trp
2. Gly, His, Ala
3. Glu, Val, Ser
4. Leu, Glu, Ser
5. Met, Ala, Gly
6. Ser, Lys, Val
7. Glu, His
8. Leu, Lys, Trp
9. Lys, Ser
10. Glu, His, Val
11. Trp, Leu, Glu
12. Ala, Met

48. Glycine has pK_a values of 2.3 and 9.6. Would you expect the pK_a values of glycylglycine to be higher or lower than these values?

49. Explain the difference in the pK_a values of the carboxyl groups of alanine, serine, and cysteine.

50. Show how valine can be prepared by
a. a Strecker synthesis. **b.** a reductive amination. **c.** an *N*-phthalimidomalonic ester synthesis.

51. Explain why the pI values of tyrosine and cysteine cannot be determined by the method described in Section 17.4.

52. Explain why the following are not found in an α-helix: two adjacent glutamates, two adjacent aspartates, or a glutamate adjacent to an aspartate.
~~~

53. Why is proline never found in an α-helix?

54. Determine the amino acid sequence of a polypeptide from the following data:

Complete hydrolysis of the peptide yields Ala, Arg, Gly, 2 Lys, Met, Phe, Pro, 2 Ser, Tyr, and Val.

Treatment with Edman's reagent releases PTH-Val.

Carboxypeptidase A releases Ala.

Treatment with cyanogen bromide yields the following two peptides:
1. Ala, 2 Lys, Phe, Pro, Ser, Tyr **2.** Arg, Gly, Met, Ser, Val

Treatment with trypsin yields the following three peptides:
1. Gly, Lys, Met, Tyr **2.** Ala, Lys, Phe, Pro, Ser **3.** Arg, Ser, Val

Treatment with chymotrypsin yields the following three peptides:
1. 2 Lys, Phe, Pro **2.** Arg, Gly, Met, Ser, Tyr, Val **3.** Ala, Ser

55. The primary structure of β-endorphin, a peptide containing 31 amino acids synthesized by the body to control pain, is shown here:

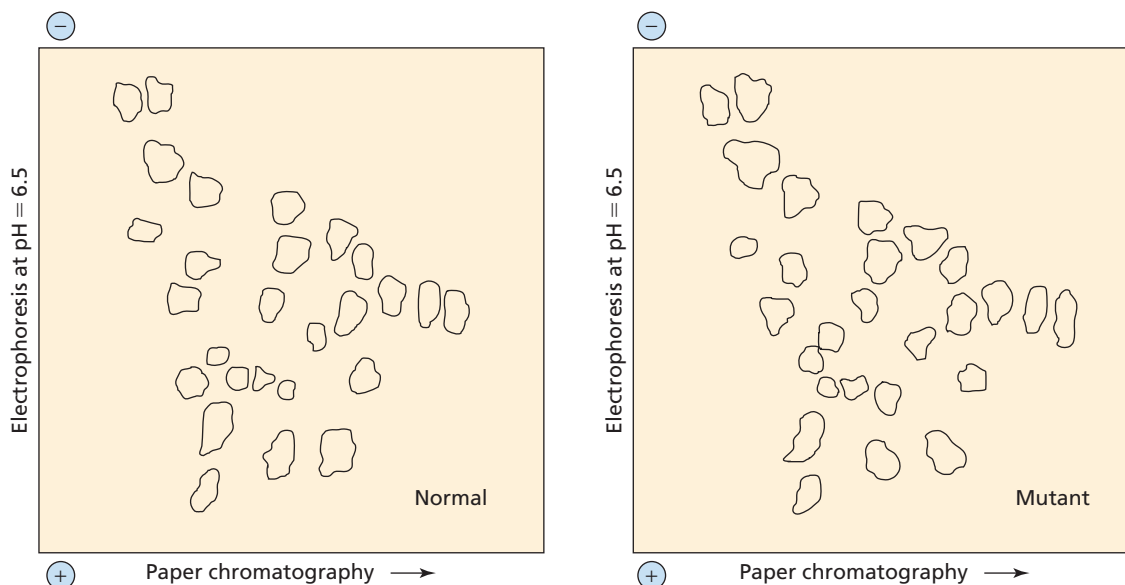
Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu

a. What fragments would be obtained as a result of treatment with
1. trypsin? **2.** cyanogen bromide? **3.** chymotrypsin?

b. How much of the primary structure could be determined if the amino acids contained in each fragment (but not their sequence) were known?

56. A chemist wanted to test his hypothesis that the disulfide bridges that form in many proteins do so after the minimum energy conformation of the protein has been achieved. He reduced a sample of an enzyme that contained four disulfide bridges and then added urea to denature the enzyme. He slowly removed these reagents so that the enzyme could re-fold and re-form the disulfide bridges. The enzyme he recovered had 80% of its original activity. What would be the percent activity in the recovered enzyme if disulfide bridge formation were entirely random rather than determined by the tertiary structure? Does this experiment support his hypothesis?

57. A normal polypeptide and a mutant of the polypeptide were hydrolyzed by an endopeptidase under the same conditions. The normal and mutant polypeptide differ by one amino acid. The fingerprints of the peptides obtained from the two polypeptides are shown here. What kind of amino acid substitution occurred as a result of the mutation? (That is, is the substituted amino acid more or less polar than the original amino acid? Is its pI lower or higher?) (*Hint*: Photocopy the fingerprints, cut them out, and overlay them.)

18

How Enzymes Catalyze Reactions • The Organic Chemistry of the Vitamins

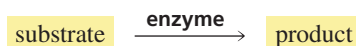
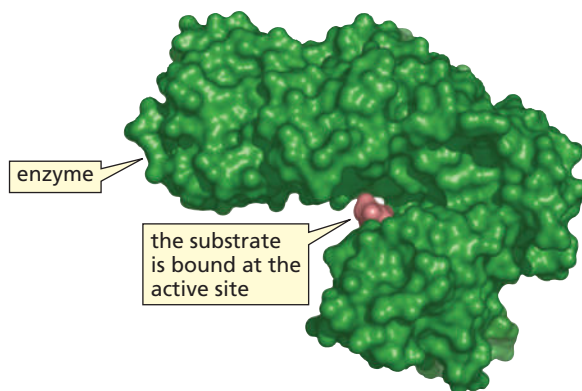
limes: vitamins A, C, K, and folate
green beans: vitamins A, B_1, B_6, C, K, folate, and riboflavin
apples: vitamins A, C, K, and folate
cucumbers: vitamins A, C, K, and pantothenate
asparagus: vitamins A, B_1, B_6, C, E, K, folate, niacin, and riboflavin

*A **vitamin** is a substance needed in a small amount for normal body function that the body cannot synthesize. In this chapter, we will look at several organic reactions occurring in cells that require the participation of a vitamin.*

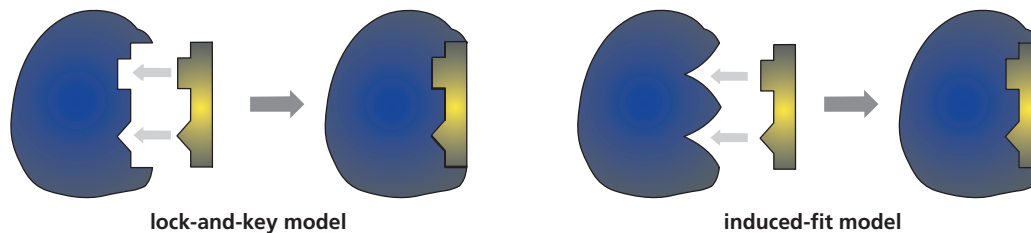
Essentially all organic reactions that occur in biological systems require a catalyst. Recall that a catalyst is a substance that increases the rate of a chemical reaction without itself being consumed or changed in the reaction (Section 5.10). Most biological catalysts are proteins (Section 17.0). Proteins that catalyze chemical reactions are called **enzymes.** Each biological reaction is catalyzed by a different enzyme. Enzymes are extraordinarily good catalysts—they can increase the rate of a reaction by as much as 10^{16}! In contrast, rate enhancements achieved by nonbiological catalysts are seldom greater than 10^4 fold.

18.1 ENZYME-CATALYZED REACTIONS

The reactant of an enzyme-catalyzed reaction is called a **substrate.**

$$\text{substrate} \xrightarrow{\textbf{enzyme}} \text{product}$$

The enzyme binds its substrate at its **active site,** a pocket in the cleft of the enzyme. All the bond-making and bond-breaking steps that convert the substrate to the product occur while the substrate is bound to the active site.

Enzymes differ from nonbiological catalysts in that they are specific for the substrate whose reaction they catalyze (Section 6.7). Enzymes have different degrees of specificity. Some enzymes are specific for a single compound. For example, glucose-6-phosphate isomerase catalyzes the isomerization of glucose-6-phosphate only. On the other hand, some enzymes catalyze the reactions of several compounds with similar structures. For instance, hexokinase catalyzes the phosphorylation of any D-hexose. The specificity of an enzyme for its substrate is another example of **molecular recognition**—the ability of one molecule to recognize another molecule.

The particular **amino acid side chains** (α-substituents) at the active site are responsible for the enzyme's specificity. For example, an amino acid with a negatively charged side chain can associate with a positively charged group on the substrate, an amino acid side chain with a hydrogen-bond donor can associate with a hydrogen-bond acceptor on the substrate, and a hydrophobic amino acid side chain can associate with hydrophobic groups on the substrate.

In 1894, Emil Fischer proposed the **lock-and-key model** to account for the specificity of an enzyme for its substrate. This model related the specificity of an enzyme for its substrate to the specificity of a lock for a correctly shaped key.

In 1958, Daniel Koshland proposed the **induced-fit model** of substrate binding. In this model, the shape of the active site does not become completely complementary to the shape of the substrate until the enzyme has bound the substrate. The energy released as a result of binding the substrate can be used to induce a change in the conformation of the enzyme, leading to more precise binding between the substrate and the active site. An example of induced fit is shown in Figure 18.1.

There is no single explanation for the remarkable catalytic ability of enzymes. Each enzyme is unique in the collection of factors it employs to catalyze a reaction. Some of the factors most enzymes have in common are the following:

- Reacting groups are brought together at the active site in the proper orientation for reaction.
- Some of the amino acid side chains of the enzyme serve as acid, base, and nucleophilic catalysts. These species are positioned relative to the substrate precisely where they are needed for catalysis.

An acid catalyst increases the rate of a reaction by donating a proton to the reactant.

A base catalyst increases the rate of a reaction by removing a proton from the reactant.

A nucleophilic catalyst increases the rate of a reaction by forming a new covalent bond with the reactant.

- Amino acid side chains can stabilize transition states and intermediates—by van der Waals interactions, electrostatic interactions, and hydrogen bonding. Recall that the more stable the species, the faster it can be formed (Section 5.7). These side chains are positioned relative to the transition state precisely where they are needed for stabilization.

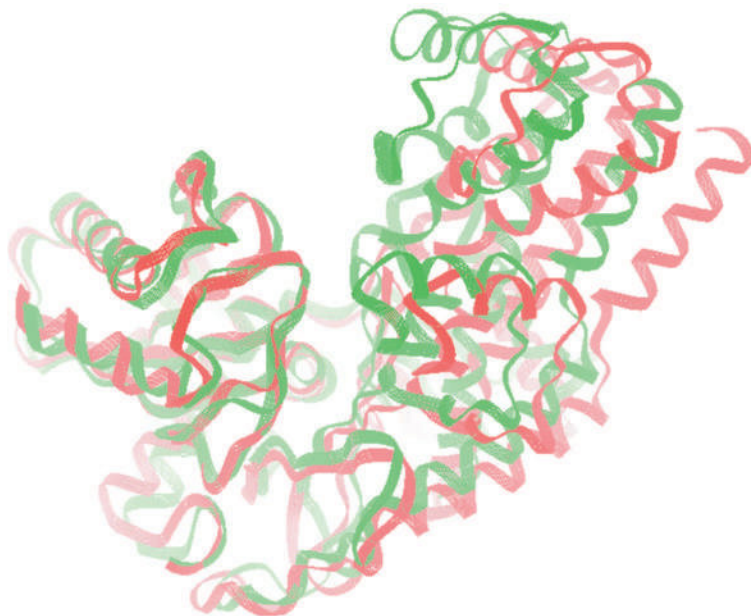



Figure 18.1
The structure of hexokinase before binding its substrate is shown in red. The structure of hexokinase after binding its substrate is shown in green.

To understand how positioning the reacting, catalytic, and stabilizing groups in the proper orientation for reaction increases the rate of a reaction, we need to look at the factors that affect the rate of a reaction.

The rate of a chemical reaction is determined by the number of molecular collisions with sufficient energy *and* with the proper orientation in a given period of time (Section 5.8):

$$\textbf{rate of reaction} = \frac{\textbf{number of collisions}}{\textbf{unit of time}} \times \begin{matrix}\textbf{fraction with}\\ \textbf{sufficient energy}\end{matrix} \times \begin{matrix}\textbf{fraction with}\\ \textbf{proper orientation}\end{matrix}$$

Therefore, if the reacting and catalytic groups are arranged at the active site of the enzyme in a way that increases the probability that they will collide with each other in the proper orientation, then the rate of the reaction will be increased. The relative rates shown in Table 18.1 demonstrate the large increase in the rate of a nonenzymatic reaction when the reacting groups are properly oriented. (**Relative rates** are obtained by dividing the rate constant for each of the reactions by the rate constant for the slowest reaction in the series.)

Reaction **A**, the first reaction in Table 18.1, is an intermolecular reaction between an ester and a carboxylate ion. Reactions **B** and **C** are intramolecular reactions; they have the same two reacting groups that **A** has but they are in the same molecule (Section 8.6). Reaction **B**, with the reacting groups tethered together so that they do not have to diffuse through the solvent to find a group with which to react, is 1000 times faster than Reaction **A**. The two functional groups in Reaction **B** are attached by a single bond. Because there is free rotation about single bonds, the two reacting groups will not always be in the proper orientation for reaction.

Table 18.1 Relative Rates of an Intermolecular Reaction and Two Intramolecular Reactions

Reaction	Relative rate
A. $CH_3C(=O)-O-C_6H_4-Br + CH_3C(=O)-O^- \longrightarrow CH_3C(=O)-O-C(=O)CH_3 + {}^-O-C_6H_4-Br$	1.0
B. $^-O-C(=O)-CH_2CH_2CH_2-C(=O)-O-C_6H_4-Br \longrightarrow$ cyclic anhydride $+ {}^-O-C_6H_4-Br$	1×10^3
C. cis $H(^-O-C(=O))C{=}C(H)C(=O)-O-C_6H_4-Br \longrightarrow$ cyclic anhydride $+ {}^-O-C_6H_4-Br$	1×10^7

In Reaction **C**, the two functional groups are attached by a double bond that prevents the reacting groups from rotating away from each other. This increases the fraction of collisions that will occur with the proper orientation: Reaction **C** is 10,000,000 times faster than Reaction **A**.

Now, you can understand why an enzyme's ability to hold all the reacting, catalytic, and stabilizing groups at the active site in the precise position needed for a reaction can lead to enormous rate enhancements.

PROBLEM 1♦

The relative rate of reaction of the cis alkene (**C**) is given in Table 18.1. What would you expect the relative rate of reaction of the trans isomer to be?

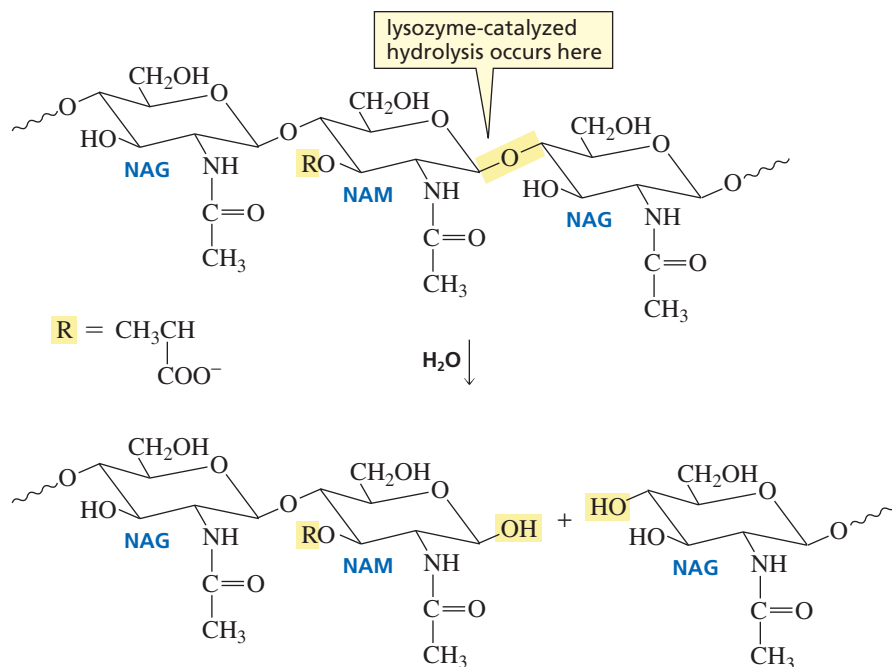
Now, we will look at the mechanisms of four enzyme-catalyzed reactions. Notice that the acid, base, and nucleophilic catalysis used by enzymes is the same as the acid, base, and nucleophilic catalysis used in organic reactions. Thus, if you refer back to sections referenced throughout this chapter, you will be able to see that much of the organic chemistry you have learned also applies to the reactions of compounds found in the biological world. The remarkable catalytic ability of enzymes stems in part from their ability to use more than one kind of catalysis (that is, acid and base, nucleophilic and acid, etc.) in the same step, which allows the reaction to occur without having to form high-energy intermediates.

18.2 AN ENZYME-CATALYZED REACTION THAT INVOLVES TWO SEQUENTIAL S_N2 REACTIONS

Lysozyme is an enzyme that destroys bacterial cell walls. These cell walls are composed of alternating *N*-acetylmuramic acid (NAM) and *N*-acetylglucosamine (NAG) units linked by β-1,4′-glycosidic linkages (Section 16.9). Lysozyme destroys the cell wall by catalyzing the hydrolysis of the NAM–NAG bond.

lysozyme-catalyzed hydrolysis occurs here

R = $CH_3CH(COO^-)$

H_2O

The active site of lysozyme binds six sugar residues of the substrate. They are labeled A, B, C, D, E, and F in Figure 18.2. The many amino acid side chains involved in binding the substrate in the correct position in the active site are also shown in Figure 18.2. The RO group of NAM cannot fit into the binding site for C or E. This means that NAM units must bind at B, D, and F. Hydrolysis occurs between D and E.

Lysozyme has two catalytic groups at the active site: Glu 35 and Asp 52. The discovery that the enzyme-catalyzed reaction takes place with retention of configuration at the anomeric carbon indicates that it cannot be a one-step S_N2 reaction. (Recall that an S_N2 reaction takes place with inversion of configuration; Section 8.1.) Therefore, the reaction must involve either two sequential S_N2 reactions or an S_N1 reaction with the enzyme blocking one face of an intermediate to nucleophilic attack. Although lysozyme was the first enzyme to have its mechanism studied—and it has been studied extensively for over 40 years—only recently have data been obtained that support the mechanism involving two sequential S_N2 reactions.

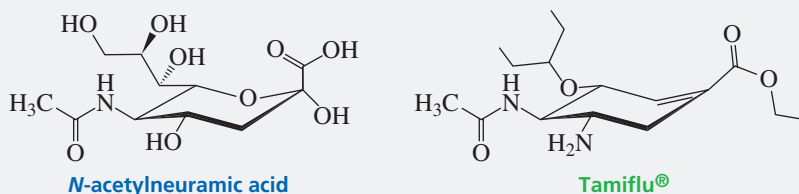
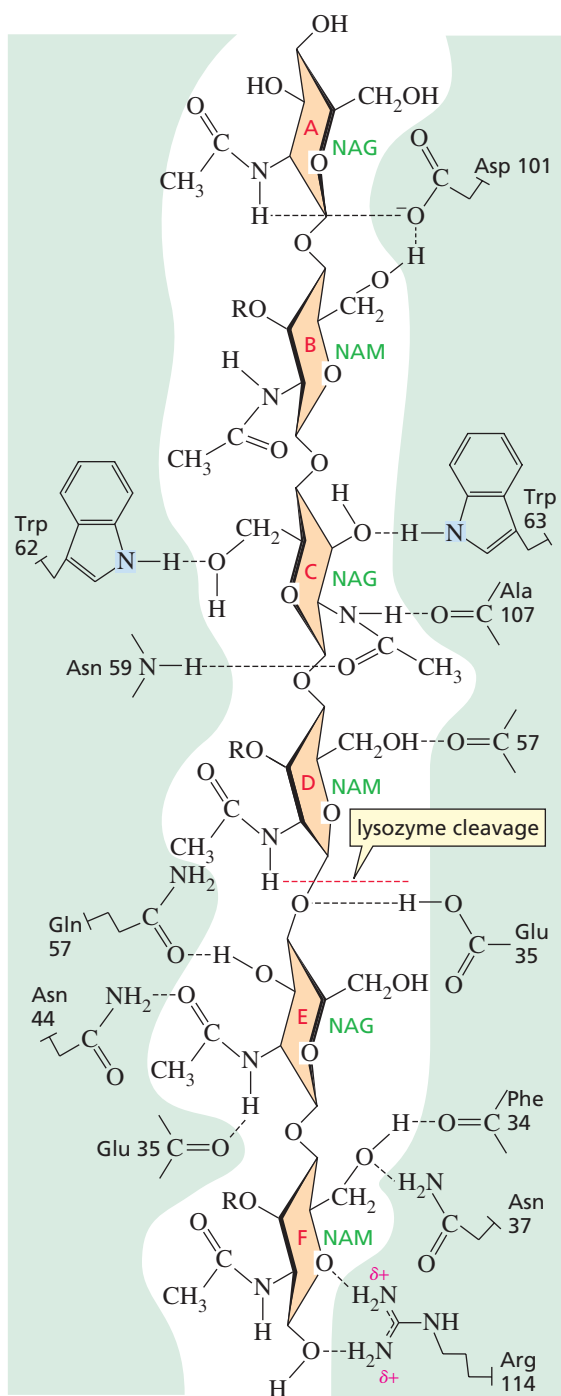
PROBLEM 2♦

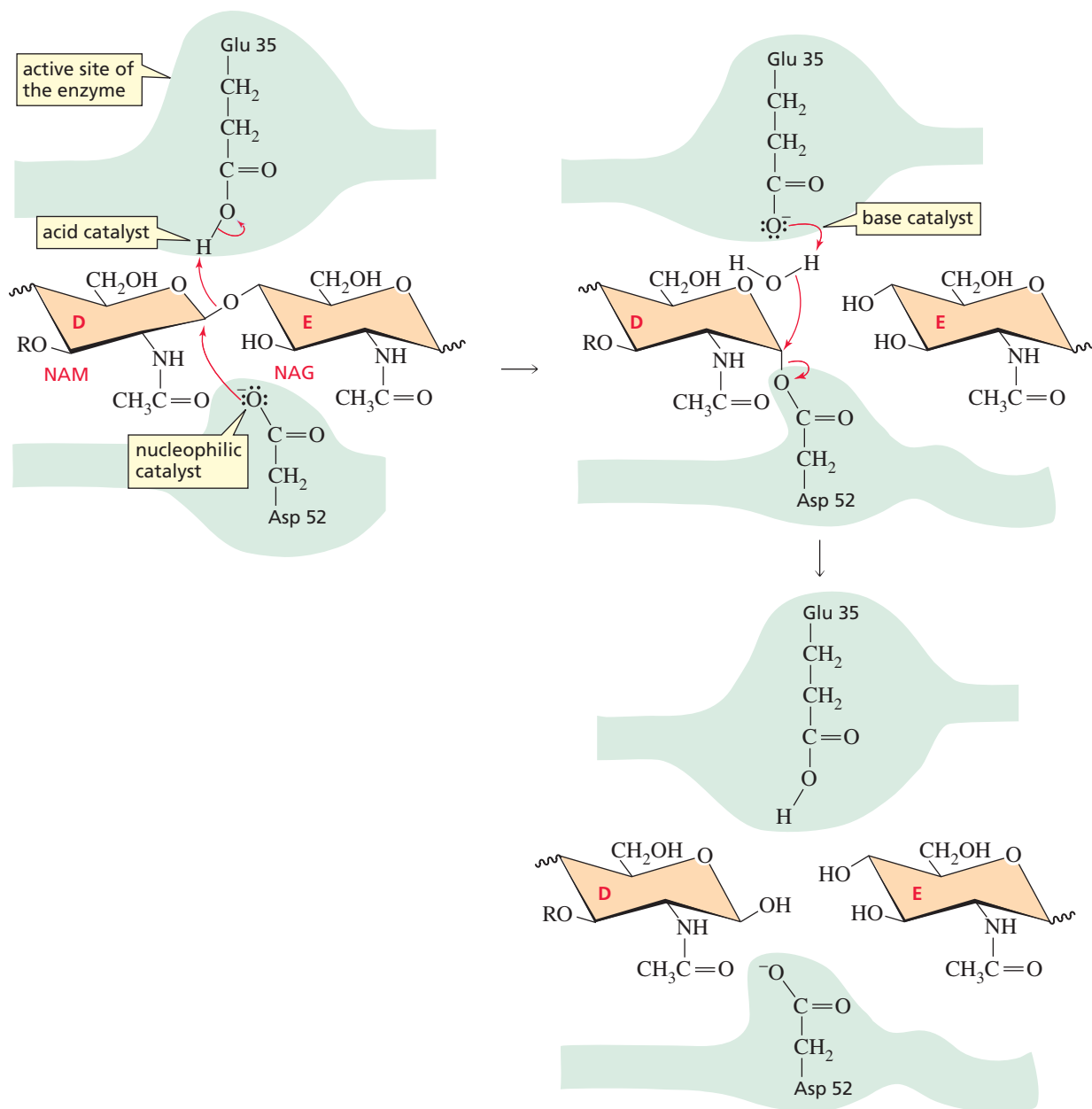
If $H_2{}^{18}O$ were used to hydrolyze lysozyme, which ring would contain the label: NAM or NAG?

How Tamiflu Works

Tamiflu is one of the few antiviral drugs currently available. It is used for the prevention and treatment of influenza A and B. Before a virus particle can be released from its host cell, an enzyme called neuraminidase must cleave off a sugar residue (*N*-acetylneuramic acid) from a glycoprotein on the surface of the cell (Section 16.11). Because *N*-acetylneuramic acid and Tamiflu have similar shapes, the enzyme cannot distinguish between them. Therefore, it can bind either one at its active site. When the enzyme binds Tamiflu, it cannot bind *N*-acetylneuramic acid. Thus, the virus particles are prevented from being released from their host cells, in which case they cannot infect new cells. Early treatment with Tamiflu is important because it will be less effective if a lot of cells have already been infected. In the past 10 years, 500 million people have been treated with Tamiflu.

***N*-acetylneuramic acid**

Tamiflu®

▲ **Figure 18.2**
The amino acids at the active site of lysozyme that are involved in binding the substrate.

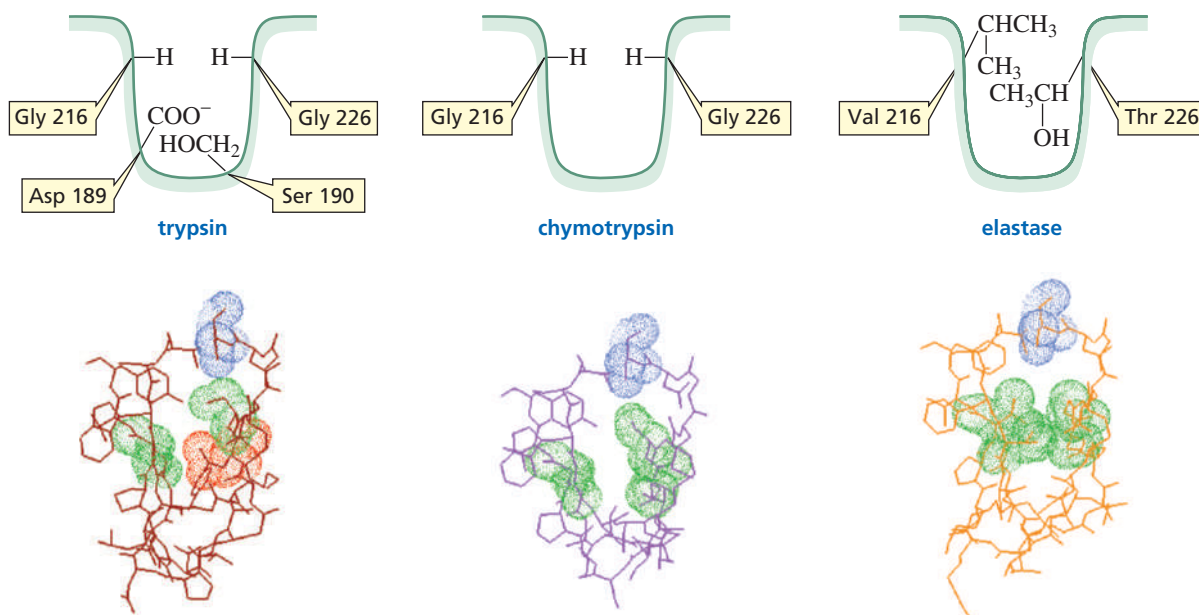
PROPOSED MECHANISM FOR THE REACTION CATALYZED BY LYSOZYME

- In the first S_N2 reaction, Asp 52 is a nucleophilic catalyst that attacks the anomeric carbon (C-1) of the NAM residue, displacing the leaving group. Glu 35 is an acid catalyst that protonates the leaving group, thereby making it a weaker base and, therefore, a better leaving group. Notice that the two catalytic groups are positioned to allow nucleophilic attack and protonation of the leaving group to occur in the same step.

  When Glu 35 is replaced by Asp, the enzyme has only weak activity. Apparently, Asp does not lie at the optimal distance from, and angle to, the oxygen atom to easily protonate it. When Glu 35 is replaced by Ala, an amino acid that cannot act as an acid catalyst, the activity of the enzyme is completely lost.

- In the second S_N2 reaction, Glu 35 is a base catalyst that increases water's nucleophilicity.

18.3 AN ENZYME-CATALYZED REACTION THAT IS REMINISCENT OF ACID-CATALYZED AMIDE AND ESTER HYDROLYSIS

Trypsin, chymotrypsin, and elastase are members of a group of *endopeptidases* known collectively as serine proteases. (Recall that an endopeptidase cleaves a peptide bond that is not at the end of a peptide chain; see Section 17.10). They are called *proteases* because they catalyze the hydrolysis of protein peptide bonds. They are called *serine proteases* because each one has a serine side chain at the active site that participates in the catalysis.

The various serine proteases have similar primary structures, suggesting that they are evolutionarily related. Although they all have the same three catalytic side chains at the active site (that is, Asp, His, and Ser), they have one important difference—namely, the composition of the pocket at the active site that binds the side chain of the amino acid in the peptide bond that undergoes hydrolysis (Figure 18.3). This pocket is what gives the serine proteases their different specificities (Section 17.10).

▲ **Figure 18.3**
The binding pockets in trypsin, chymotrypsin, and elastase. The negatively charged aspartate is shown in red, the relatively nonpolar amino acids are shown in green, and an amino acid at the top of the pocket is shown in blue. The structures of the binding pockets explain why trypsin binds long, positively charged amino acids; chymotrypsin binds flat, nonpolar amino acids; and elastase binds only small amino acids.

The pocket in trypsin is narrow and has a serine and a negatively charged aspartate carboxyl group at its bottom. The shape and charge of the binding pocket cause it to bind long, positively charged amino acid side chains (Lys and Arg). This is why trypsin hydrolyzes only peptide bonds on the C-side of arginine and lysine. The pocket in chymotrypsin is narrow and is lined with nonpolar amino acids, so chymotrypsin cleaves on the C-side of amino acids with flat, nonpolar side chains (Phe, Tyr, and Trp).

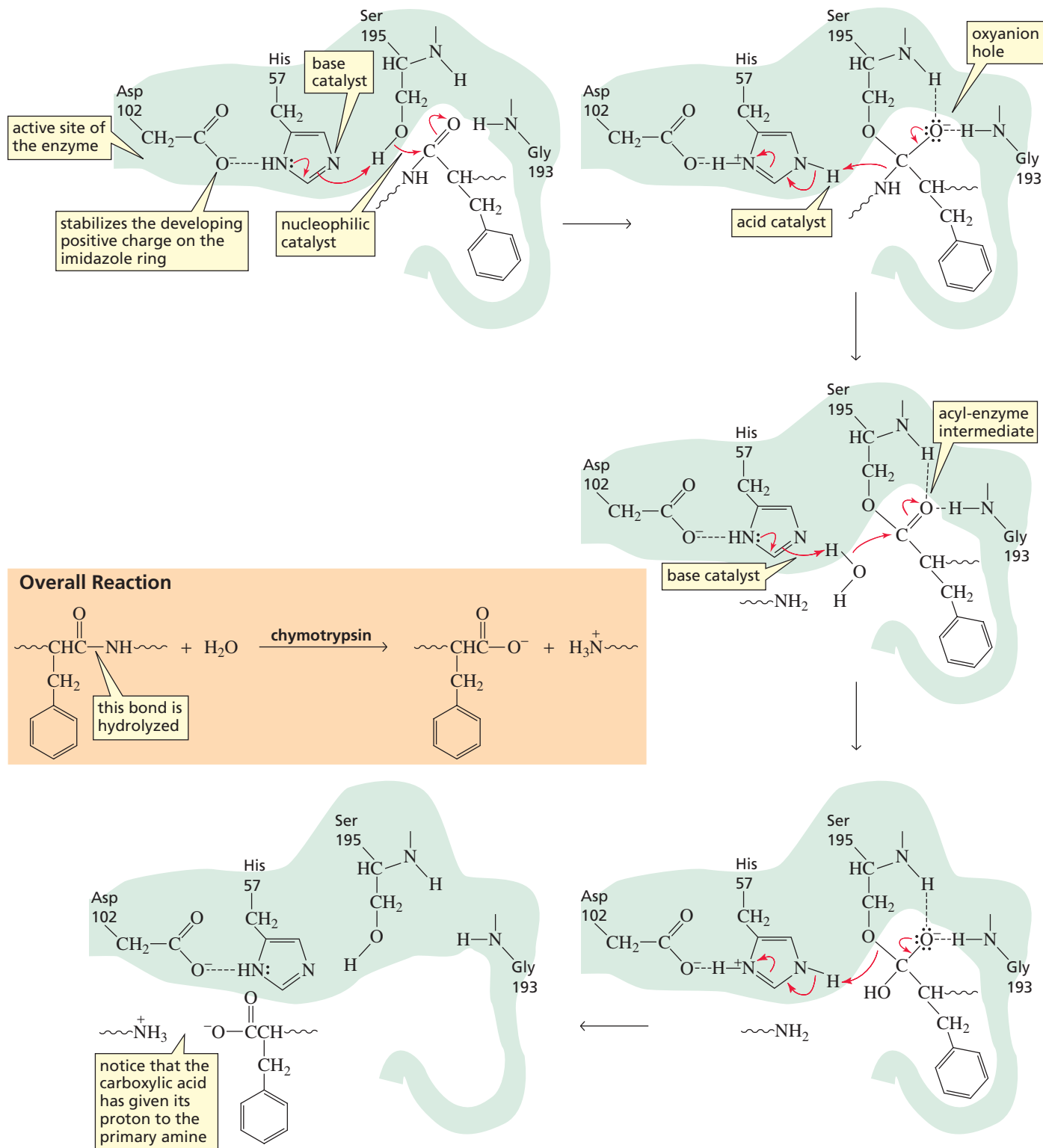
In elastase, two glycines on the sides of the pocket in trypsin and in chymotrypsin are replaced by relatively bulky valine and threonine. Consequently, only small amino acids can fit into the pocket. Elastase, therefore, hydrolyzes peptide bonds on the C-side of small amino acids (Gly, Ala, Ser, and Val).

The proposed mechanism for the chymotrypsin-catalyzed hydrolysis of a peptide bond is shown here. Notice that it involves two successive nucleophilic acyl substitution reactions: first, nucleophilic addition to an amide to form a tetrahedral intermediate followed by elimination from the tetrahedral intermediate; and then, nucleophilic addition to an ester to form a tetrahedral intermediate followed by elimination from the tetrahedral intermediate (Section 11.4). The other serine proteases follow the same mechanism.

PROPOSED MECHANISM FOR THE REACTION CATALYZED BY SERINE PROTEASES

Overall Reaction

$$\sim CH(CH_2C_6H_5)C(=O)-NH\sim + H_2O \xrightarrow{\text{chymotrypsin}} \sim CH(CH_2C_6H_5)C(=O)-O^- + H_3\overset{+}{N}\sim$$

this bond is hydrolyzed

- As a consequence of binding the flat, nonpolar side chain in the hydrophobic pocket, the amide linkage to be hydrolyzed is positioned very close to Ser 195. His 57 is a base catalyst, increasing the nucleophilicity of the serine that adds to the carbonyl group. This step is helped by Asp 102, which uses its negative charge to stabilize the developing positive charge on His 57 and to position the five-membered ring so that its basic N atom is close to the OH group of serine. The stabilization of a charge by an opposite charge is called **electrostatic catalysis.** Formation of the tetrahedral intermediate causes a slight change in the conformation of the protein. This allows the negatively charged oxygen

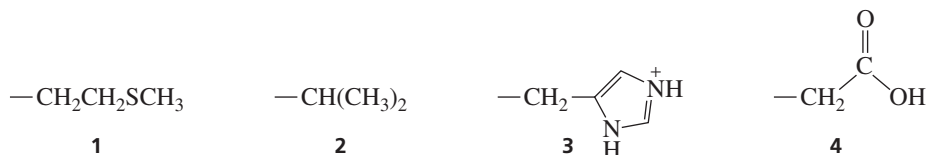
to slip into a previously unoccupied area of the active site known as the *oxyanion hole*. Once in the oxyanion hole, the negatively charged oxygen can hydrogen bond with two peptide groups (Gly 193 and Ser 195), which stabilizes the tetrahedral intermediate.

- In the next step, the tetrahedral intermediate collapses, eliminating the amino group. This is a strongly basic group that cannot be eliminated without the participation of His 57, an acid catalyst that increases the leaving propensity of the group by protonating it—thereby making it a weaker base and, therefore, a better leaving group. The product of the second step is an **acyl-enzyme intermediate** because the serine group of the enzyme has been acylated—that is, an acyl group has been put on it.
- The third step is just like the first step, except that water instead of serine is the nucleophile. Water adds to the acyl group of the acyl-enzyme intermediate, with His 57 acting as a base catalyst to increase water's nucleophilicity, and Asp 102 again stabilizing the positively charged histidine side chain.
- In the final step, the tetrahedral intermediate collapses, eliminating serine. His 57 is an acid catalyst in this step, increasing serine's leaving propensity. (Note that in this last step, the carboxylic acid product loses a proton and the amine product gains a proton, because the amine is a stronger base than the carboxylate ion.)

Notice that the first two steps are alcoholysis of an amide and the second two steps are hydrolysis of an ester. Each of these two-step reactions requires six steps in the non-enzymatic reactions (Sections 11.10 and 11.16). As a result of holding the reacting and catalytic groups that participate in the reaction precisely where they need to be, several steps can occur simultaneously.

PROBLEM 3 Solved

Which of the following amino acid side chains can aid the departure of a leaving group?

$—CH_2CH_2SCH_3$ **1** $—CH(CH_3)_2$ **2** $—CH_2$–(imidazolium, $\overset{+}{N}H$, NH) **3** $—CH_2C(=O)OH$ **4**

Solution Side chains **1** and **2** do not have an acidic proton, so they cannot aid the departure of a leaving group by protonating it. Side chains **3** and **4** each have an acidic proton, so they can aid in the departure of a leaving group.

PROBLEM 4♦

Arginine and lysine side chains fit into trypsin's binding pocket (Figure 18.3). One of these side chains forms a direct hydrogen bond with serine and an indirect hydrogen bond (mediated through a water molecule) with aspartate. The other side chain forms direct hydrogen bonds with both serine and aspartate. Which is which?

18.4 AN ENZYME-CATALYZED REACTION THAT IS REMINISCENT OF THE BASE-CATALYZED ENEDIOL REARRANGEMENT

Glycolysis is the name given to the series of enzyme-catalyzed reactions responsible for converting glucose into two molecules of pyruvate (Section 19.5). The second reaction in glycolysis is an isomerization reaction that converts glucose-6-phosphate to fructose-6-phosphate. Recall that glucose is an aldohexose, whereas fructose is a ketohexose, so the enzyme that catalyzes this reaction—glucose-6-phosphate isomerase—converts an aldose to a ketose. Notice that steps 2 and 3 of the mechanism are the same as the mechanism for the enediol rearrangement except that there are two steps in the enzyme-catalyzed reaction rather than four (Section 16.5). There are fewer steps because, since the reactant and the catalysts are precisely where they need to be, acid and base catalysis can occur in the same step rather than in separate steps, thereby avoiding the formation of relatively unstable negatively charged intermediates.

PROPOSED MECHANISM FOR THE REACTION CATALYZED BY GLUCOSE-6-PHOSPHATE ISOMERASE

acid catalyst

active site of the enzyme

base catalyst

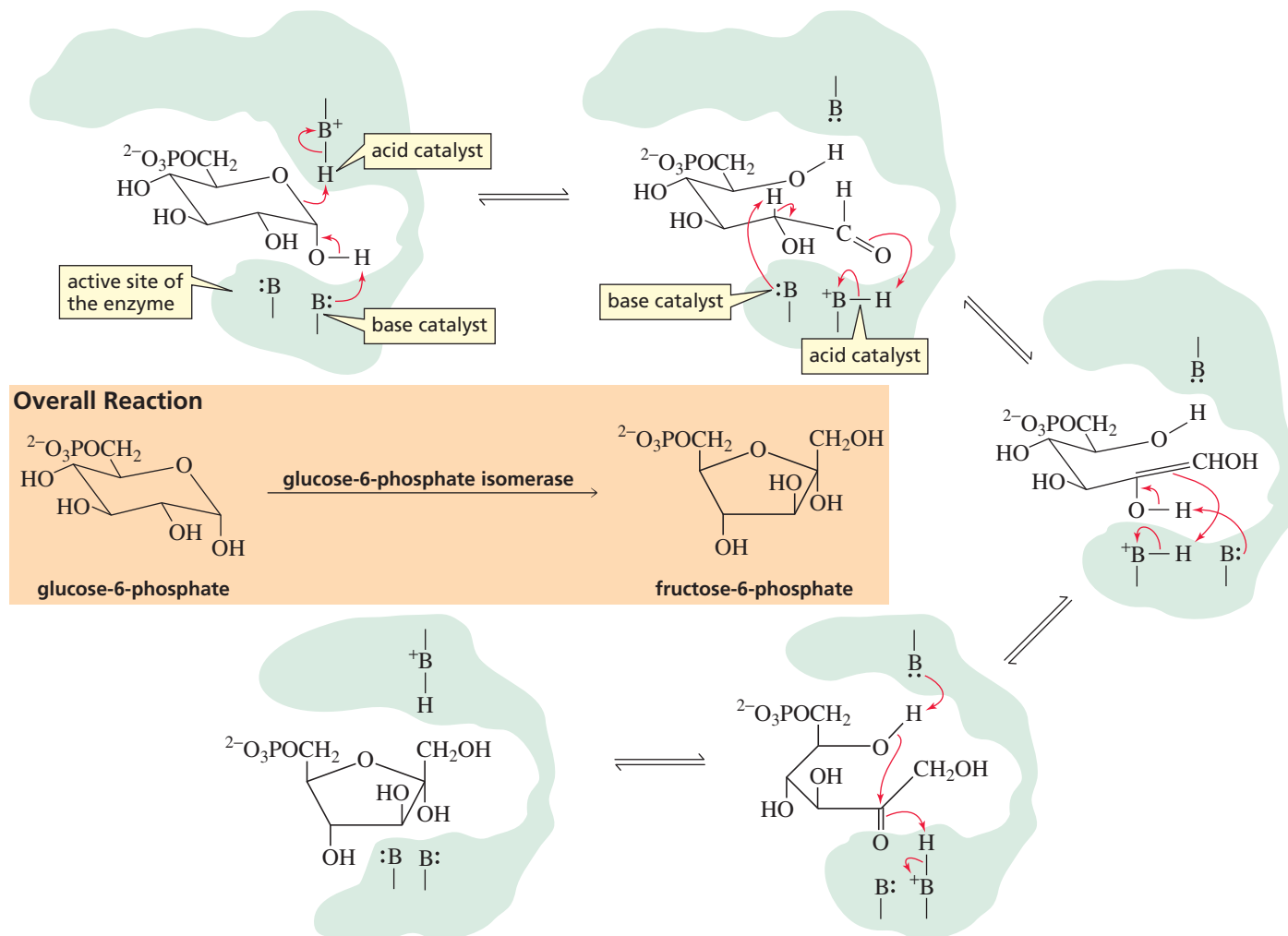
base catalyst

acid catalyst

Overall Reaction

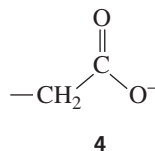
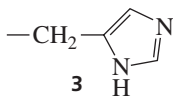
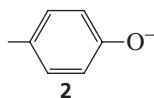
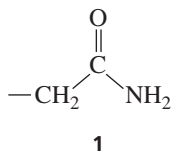
glucose-6-phosphate isomerase

glucose-6-phosphate

fructose-6-phosphate

- The first step is a ring-opening reaction of a hemiacetal (Section 16.6). A base catalyst removes a proton from the OH group, and an acid catalyst aids the departure of the leaving group by protonating it, thereby making it a weaker base and, therefore, a better leaving group.
- In the second step, a base catalyst removes a proton from the α-carbon of the aldehyde and an acid catalyst protonates the oxygen, forming an enediol. Recall that the α-hydrogen of an aldehyde is relatively acidic (Section 13.1).
- In the next step, the enediol is converted to a ketone.
- In the final step, the conjugate base of the acid catalyst employed in the first step and the conjugate acid of the base catalyst employed in the first step catalyze ring closure.

PROBLEM 5♦

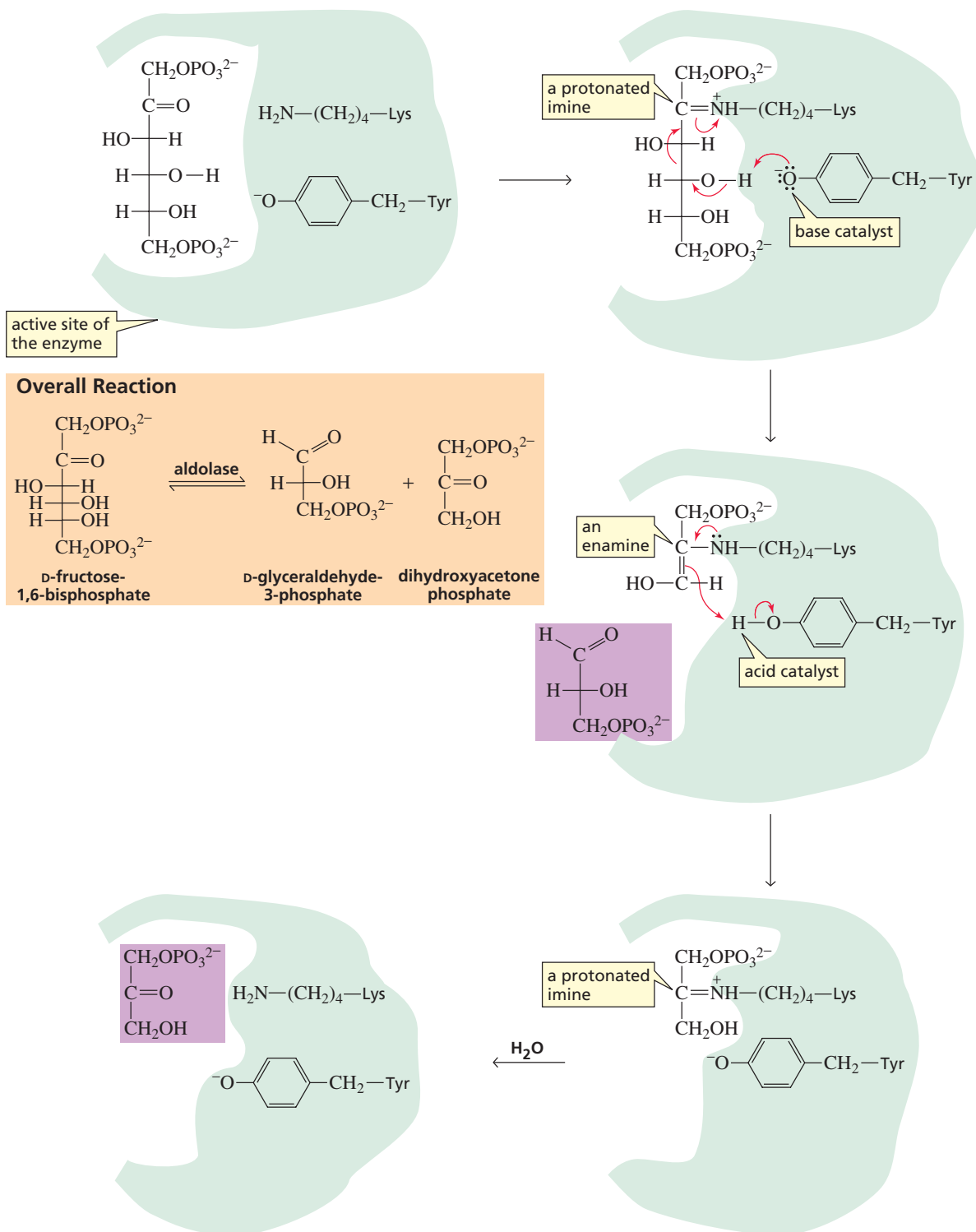
Which of the following amino acid side chains can help remove a proton from the α-carbon of an aldehyde?

1: $-CH_2-C(=O)-NH_2$ 2: phenyl-O^- 3: $-CH_2$-imidazole 4: $-CH_2-C(=O)-O^-$

PROBLEM 6

When glucose undergoes base-catalyzed isomerization in the absence of an enzyme, mannose is one of the products that is formed (Section 16.5). Why is mannose not formed in the enzyme-catalyzed reaction?

18.5 AN ENZYME-CATALYZED REACTION THAT IS REMINISCENT OF A RETRO-ALDOL ADDITION

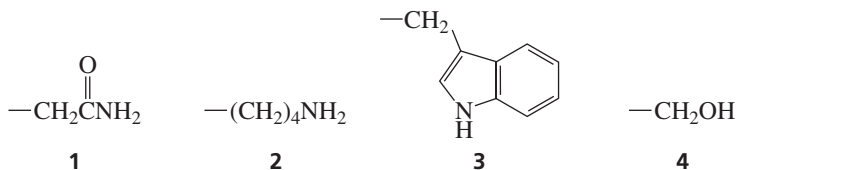
The substrate for the first enzyme-catalyzed reaction in the series of reactions known as glycolysis is D-glucose (a six-carbon compound). The final product of glycolysis is two molecules of pyruvate (a three-carbon compound). Therefore, at some point in the series of enzyme-catalyzed reactions, a six-carbon compound must be cleaved into two

PROPOSED MECHANISM FOR THE REACTION CATALYZED BY ALDOLASE

three-carbon compounds. The enzyme *aldolase* catalyzes this cleavage. (Aldolase converts *fructose-1,6-bisphosphate* into *glyceraldehyde-3-phosphate* and *dihydroxyacetone phosphate*. The enzyme is called aldolase because the reaction it catalyzes is a retro-aldol addition—that is, it is the reverse of an aldol addition (Section 13.5).

- In the first step, fructose-1,6-bisphosphate forms a protonated imine with a lysine side chain at the active site of the enzyme (Section 12.8).
- In the next step, the bond between C-3 and C-4 is broken, with tyrosine acting as a base catalyst. The molecule of glyceraldehyde-3-phosphate (one of the three-carbon products) formed in this step dissociates from the enzyme.
- The intermediate rearranges to a protonated imine, with the tyrosine side chain now acting as an acid catalyst.
- Hydrolysis of the protonated imine releases dihydroxyacetone phosphate, the other three-carbon product.

PROBLEM 7♦

Which of the following amino acid side chains can form an imine with a substrate?

$—CH_2C(=O)NH_2$ **1** $—(CH_2)_4NH_2$ **2** $—CH_2$–(indol-3-yl, N–H) **3** $—CH_2OH$ **4**

PROBLEM 8

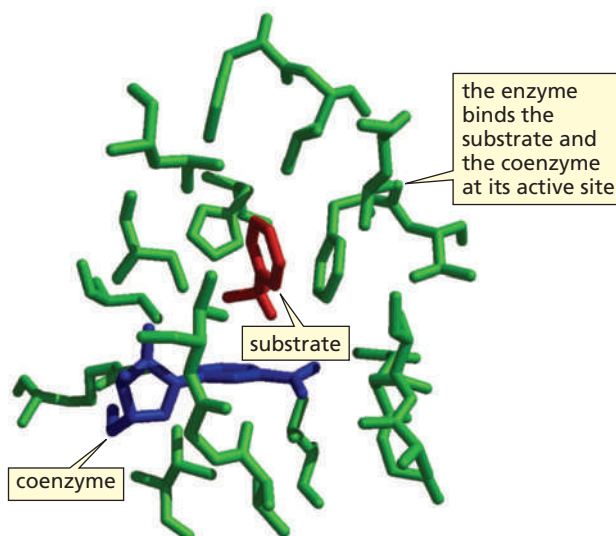
Draw the mechanism for the hydroxide-ion-catalyzed cleavage of fructose-1,6-bisphosphate.

PROBLEM 9

What advantage does the enzyme gain by forming an imine?

18.6 VITAMINS AND COENZYMES

Many enzymes cannot catalyze a reaction without the help of a **coenzyme.** Coenzymes are derived from organic compounds commonly known as *vitamins*. A **vitamin** is a substance needed in a small amount for normal body function that the body cannot synthesize. The first substance recognized to be essential in the diet was an amine (vitamin B_1), which led scientists to conclude incorrectly that all such compounds were amines. As a result, they were originally called vitamines ("amines required for life"). The *e* was later dropped from the name. Table 18.2 lists the vitamins and their chemically active coenzyme forms.

We have seen that the acids, bases, and nucleophiles that catalyze organic reactions in the laboratory are similar to the acidic, basic, and nucleophilic side chains that enzymes use to catalyze organic reactions that occur in cells (Sections 18.2–18.5). Now, we will see that coenzymes play a variety of chemical roles that the amino acid side chains of enzymes cannot play. Some coenzymes function as oxidizing agents, some are reducing agents, some allow electrons to be delocalized, some activate groups for further reaction, and some provide good nucleophiles or strong bases needed for a particular reaction.

Because it would be highly inefficient for the body to use a compound only once and then discard it, coenzymes are recycled. Therefore, we will see that any coenzyme that is changed during the course of a reaction is subsequently converted back to its original form.

Early nutritional studies divided vitamins into two classes: water-soluble vitamins and water-insoluble vitamins (Table 18.2).

Table 18.2 The Vitamins, the Coenzymes for Which They Are Precursors, and the Chemical Functions of the Coenzymes

Vitamin	Coenzyme	Reaction catalyzed	Human deficiency disease
Water-Soluble Vitamins			
Niacin (vitamin B_3)	NAD^+, $NADP^+$	Oxidation	Pellagra
	NADH, NADPH	Reduction	
Riboflavin (vitamin B_2)	FAD	Oxidation	Skin inflammation
	$FADH_2$	Reduction	
Thiamine (vitamin B_1)	Thiamine pyrophosphate (TPP)	Acyl group transfer	Beriberi
Lipoic acid (lipoate)	Lipoate	Oxidation	—
	Dihydrolipoate	Reduction	
Pantothenic acid (vitamin B_5)	Coenzyme A (CoASH)	Acyl group transfer	—
Biotin (vitamin H or vitamin B_7)	Biotin	Carboxylation	—
Pyridoxine (vitamin B_6)	Pyridoxal phosphate (PLP)	Decarboxylation	Anemia
		Transamination	
		Racemization, and other reactions of amino acids	
Vitamin B_{12}	Coenzyme B_{12}	Isomerization	Pernicious anemia
Folic acid	Tetrahydrofolate (THF)	One-carbon transfer	Megaloblastic anemia
Ascorbic acid (vitamin C)	—	—	Scurvy
Water-Insoluble Vitamins			
Vitamin A	—	—	—
Vitamin D	—	—	Rickets
Vitamin E	—	—	—
Vitamin K	Vitamin KH_2	Carboxylation	—

Vitamin K is the only *water-insoluble vitamin* currently known to be a precursor of a coenzyme. Vitamin A is required for proper vision, vitamin D regulates calcium and phosphate metabolism, and vitamin E is an antioxidant. Because they do not function as coenzymes, these vitamins are not discussed in this chapter. (Vitamins A and E are discussed in Sections 4.1 and 14.7.)

All the *water-soluble vitamins* except vitamin C are precursors of coenzymes. In spite of its name, vitamin C is not a vitamin because it is required in fairly high amounts and most mammals are able to synthesize it (Section 16.6). Primates and guinea pigs cannot synthesize it, however, so it must be included in their diets. We have seen that vitamins C and E are radical inhibitors and, therefore, are antioxidants: vitamin C traps radicals formed in aqueous environments, whereas vitamin E traps radicals formed in nonpolar environments (Section 14.7).

It is difficult to overdose on water-soluble vitamins because the body can generally eliminate any excess. One can, however, overdose on water-insoluble vitamins because they are *not* easily eliminated by the body and can accumulate in cell membranes and other nonpolar components of the body. Excess vitamin D, for example, causes calcification of soft tissues. The kidneys are particularly susceptible to calcification, which

eventually leads to kidney failure. Vitamin D is formed in the skin as a result of a photochemical reaction caused by the ultraviolet rays from the sun. Because of the current, widespread use of sunscreens, a significant number of children are being found to have a vitamin D deficiency.

Vitamin B_1

Christiaan Eijkman (1858–1930) was a member of a medical team that was sent to the East Indies to study an outbreak of beriberi in 1886. At that time, all diseases were thought to be caused by microorganisms. When the microorganism that caused beriberi could not be found, the team left the East Indies but Eijkman stayed behind to become the director of a new bacteriological laboratory. There, in 1896, Eijkman accidentally discovered the cause of the disease when he noticed that laboratory chickens had developed the symptoms characteristic of beriberi. He found that the symptoms had appeared when a cook started feeding the chickens polished (white) rice meant for hospital patients. The symptoms disappeared when a new cook resumed giving brown rice to the chickens. Later it was recognized that thiamine (vitamin B_1) is present in rice husks, which are removed when the rice is polished.

18.7 NIACIN: THE VITAMIN NEEDED FOR MANY REDOX REACTIONS

Any enzyme that catalyzes an oxidation or a reduction reaction requires a coenzyme because none of the amino acid side chains are oxidizing or reducing agents. The coenzyme serves as the oxidizing or reducing agent. The enzyme's role is to hold the substrate and coenzyme together so that the oxidation or reduction reaction can take place (see the model on page 13).

The Pyridine Nucleotide Coenzymes

The coenzyme most commonly used by enzymes to catalyze an oxidation reaction is **nicotinamide adenine dinucleotide (NAD^+).** The coenzyme most commonly used to catalyze a reduction reaction is reduced **nicotinamide adenine dinucleotide phosphate (NADPH).**

substituted pyridine

nicotinamide

responsible for the "+" in NAD^+

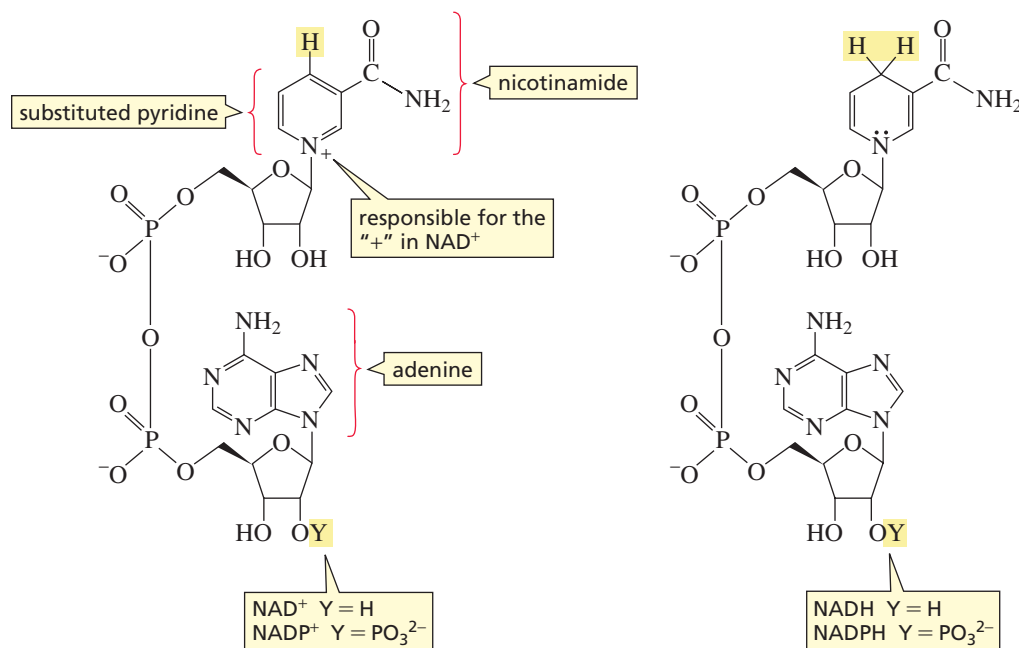
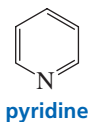
adenine

NAD^+ Y = H
$NADP^+$ Y = PO_3^{2-}

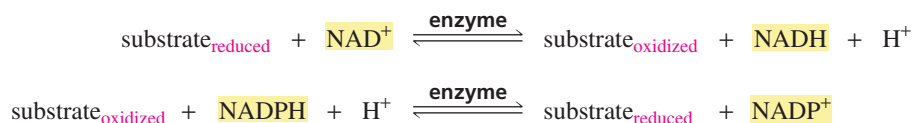
NADH Y = H
NADPH Y = PO_3^{2-}

NAD^+ is an oxidizing agent.

NADPH is a reducing agent.

pyridine

When NAD^+ oxidizes a substrate, the coenzyme is reduced to NADH. When NADPH reduces a substrate, it is oxidized to $NADP^+$. Enzymes that catalyze oxidation reactions bind NAD^+ more tightly than they bind NADH. Once the oxidation reaction is completed, the relatively loosely bound NADH dissociates from the enzyme. Similarly, enzymes that catalyze reduction reactions bind NADPH more tightly than they bind $NADP^+$. Once the reduction reaction is complete, the relatively loosely bound $NADP^+$ dissociates from the enzyme. Because each of the coenzymes has a pyridine ring, they are known as the **pyridine nucleotide coenzymes.**

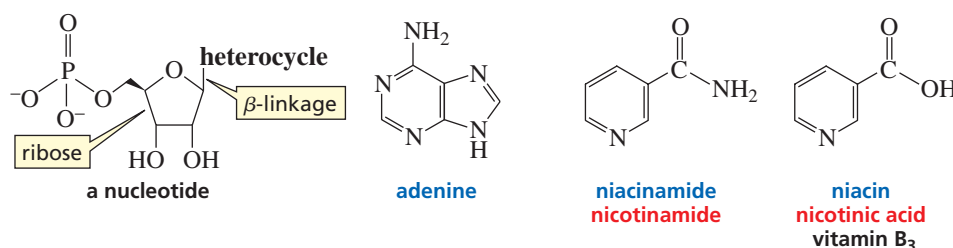
$$\text{substrate}_{\text{reduced}} + NAD^+ \underset{}{\overset{\text{enzyme}}{\rightleftharpoons}} \text{substrate}_{\text{oxidized}} + NADH + H^+$$

$$\text{substrate}_{\text{oxidized}} + NADPH + H^+ \underset{}{\overset{\text{enzyme}}{\rightleftharpoons}} \text{substrate}_{\text{reduced}} + NADP^+$$

NAD^+ is composed of two nucleotides linked together through their phosphate groups. A **nucleotide** consists of a heterocyclic compound attached, in a β-linkage, to C-1 of a phosphorylated ribose (Section 21.1). A **heterocyclic compound** has one or more ring atoms that are not carbons.

heterocycle
β-linkage
ribose
a nucleotide

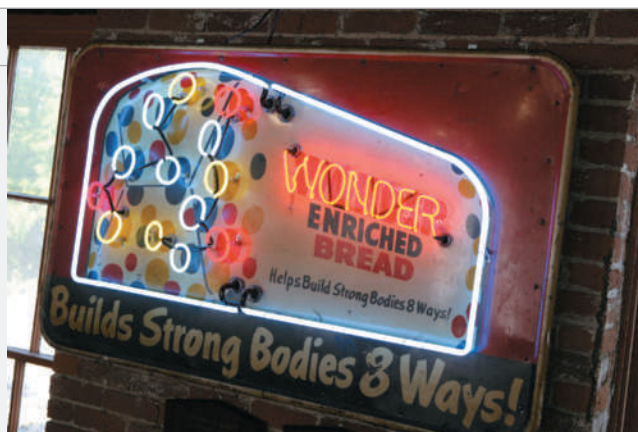
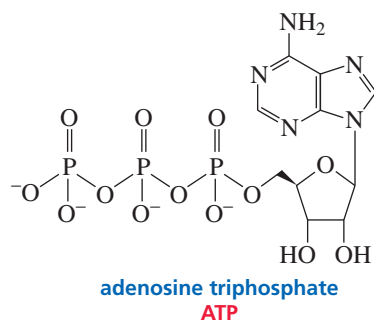
adenine

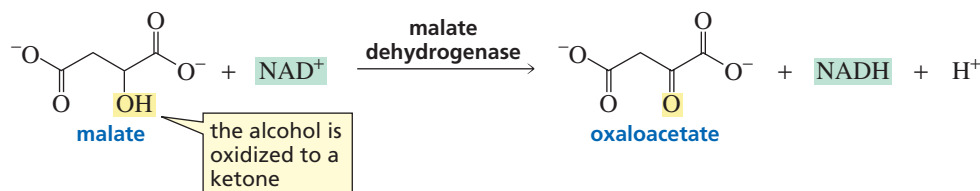
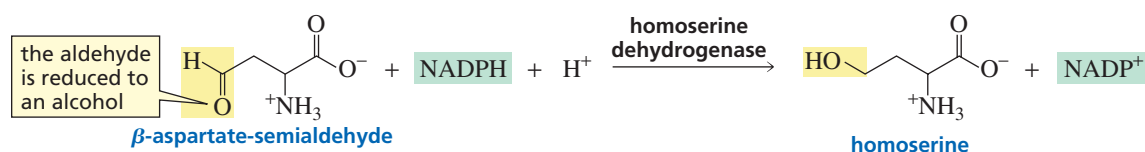
niacinamide
nicotinamide

niacin
nicotinic acid
vitamin B_3

The heterocyclic component of one of the nucleotides of NAD^+ is nicotinamide, and the heterocyclic component of the other is adenine. This accounts for the coenzyme's name (**n**icotinamide **a**denine **d**inucleotide). The positive charge in the NAD^+ abbreviation indicates the positively charged nitrogen of the pyridine ring. $NADP^+$ differs from NAD^+ only in having a phosphate group bonded to the 2′-OH group of the ribose of the adenine nucleotide—hence the addition of "P" to the name.

Niacin Deficiency

A deficiency in niacin causes pellagra, a disease that begins with dermatitis and ultimately causes insanity and death. More than 120,000 cases of pellagra were reported in the United States in 1927, mainly among poor people with unvaried diets. A factor known to be present in preparations of vitamin B_3 prevented pellagra, but it was not until 1937 that the factor was identified as nicotinic acid. Mild deficiencies slow down metabolism, which is a potential contributing factor in obesity.

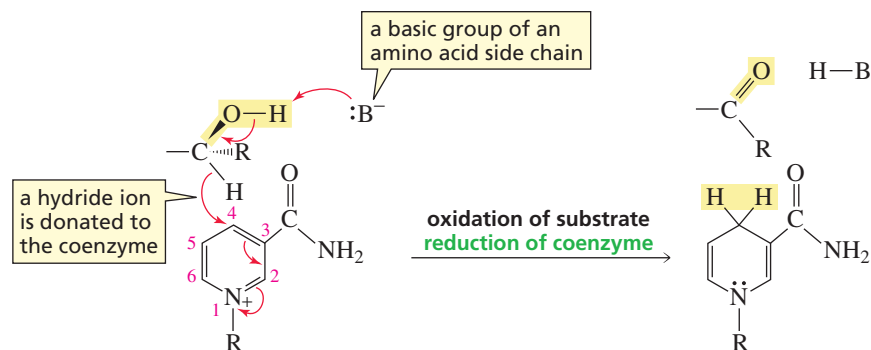
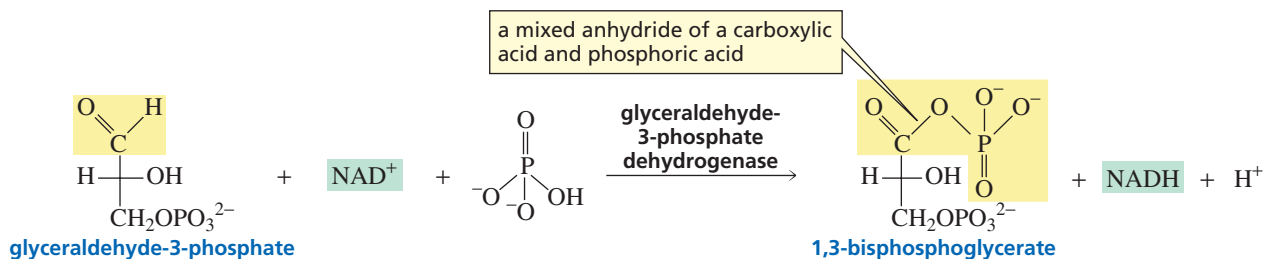
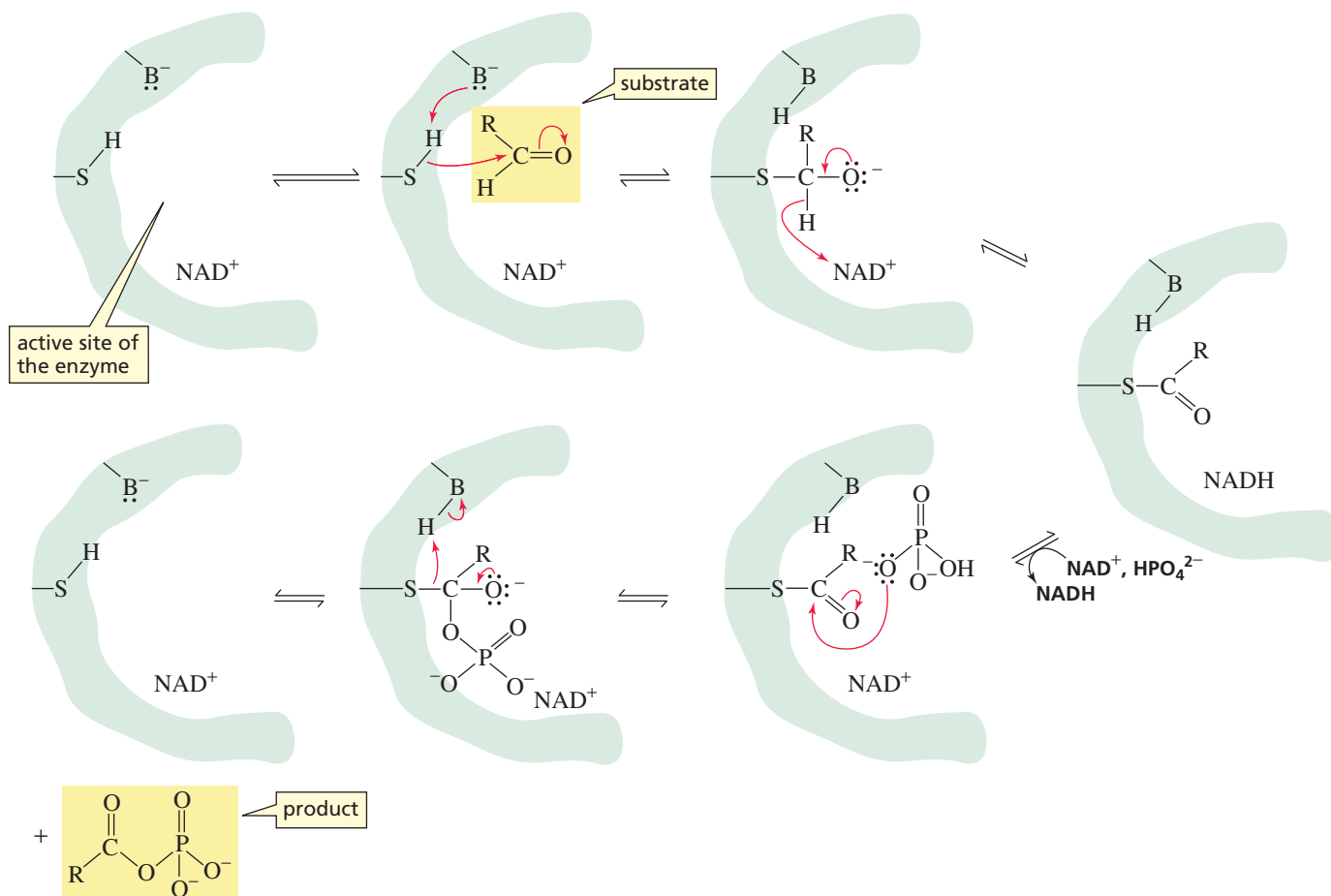
When bread companies started adding nicotinic acid to their bread, they insisted that its name be changed to niacin because nicotinic acid sounded too much like nicotine and they did not want their vitamin-enriched bread to be associated with a harmful substance.

The adenine nucleotide for the coenzymes is provided by ATP. Niacin (also known as vitamin B_3) is the portion of the coenzyme that the body cannot synthesize and must acquire through the diet. (Humans can synthesize a small amount of vitamin B_3 from the amino acid tryptophan but not enough to meet the body's metabolic needs.)

NAD^+ and NADH are generally used as coenzymes in **catabolic reactions**—that is, in biological reactions that break down complex biomolecules in order to provide the cell with energy. $NADP^+$ and NADPH are generally used as coenzymes in **anabolic reactions**—that is, in biological reactions involved in synthesizing complex biomolecules (Section 19.0).

Malate dehydrogenase is the enzyme that catalyzes the oxidation of the *secondary alcohol group* of malate to a *ketone* (Section 9.5) in the citric acid cycle, a catabolic pathway. The oxidizing agent in this reaction is NAD^+. Most enzymes that catalyze oxidation reactions are called *dehydrogenases*. In other words, dehydrogenases remove hydrogen.

β-Aspartate-semialdehyde is reduced to homoserine in an anabolic pathway. NADPH is the reducing agent.

The differentiation between the coenzymes used in catabolism and those used in anabolism results from the strong specificity that each of the enzymes that catalyze these oxidation–reduction reactions exhibits for a particular coenzyme. For example, an enzyme that catalyzes an oxidation reaction can readily tell the difference between NAD^+ and $NADP^+$; if the enzyme is in a catabolic pathway, it will bind NAD^+ but not $NADP^+$.

The relative concentrations of the coenzymes in a cell also encourage the appropriate coenzyme to be bound. For example, catabolic reactions are predominantly oxidation reactions, and anabolic reactions are predominantly reduction reactions. The cell maintains its $[NAD^+]/[NADH]$ ratio near 1000 and its $[NADP^+]/[NADPH]$ ratio at about 0.01. Thus, NAD^+ is the oxidizing coenzyme and NADPH is the reducing coenzyme most available in a cell.

How Does NAD^+ Oxidize a Substrate?

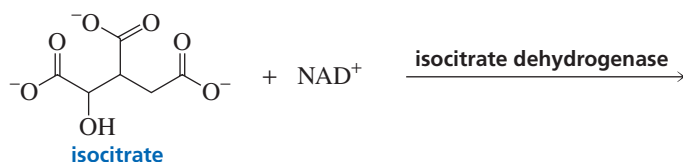
All the chemistry of the pyridine nucleotide coenzymes takes place at the 4-position of the pyridine ring. The purpose of the rest of the molecule is to recognize and bind to the active site of the enzyme.

A substrate that is being *oxidized* donates a hydride ion (H^-) to the 4-position of the pyridine ring. In the following reaction, for example, a secondary alcohol is oxidized to a ketone. A basic amino acid side chain of the enzyme can help the reaction by removing a proton from the oxygen atom of the substrate. (In the mechanisms shown in this chapter, HB and $:B^-$ represent amino acid side chains at the active site of the enzyme that can provide a proton or remove a proton, respectively.)

Glyceraldehyde-3-phosphate dehydrogenase is another enzyme that uses NAD^+ to oxidize a substrate. The enzyme catalyzes the oxidation of the aldehyde group of glyceraldehyde-3-phosphate to a mixed anhydride of a carboxylic acid and phosphoric acid.

MECHANISM FOR THE REACTION CATALYZED BY GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE (GAPDH)

- The enzyme binds the substrate (glyceraldehyde-3-phosphate) at its active site.
- An SH group (a nucleophile) of a cysteine side chain adds to the carbonyl carbon of glyceraldehyde-3-phosphate to form a tetrahedral intermediate. A basic enzyme side chain increases cysteine's nucleophilicity by removing a proton.
- The tetrahedral intermediate eliminates a hydride ion, transferring it to the 4-position of the pyridine ring of NAD^+ that is bound to the enzyme at an adjacent site, forming NADH.
- NADH dissociates from the enzyme, and the enzyme binds a new NAD^+. (How NADH is oxidized back to NAD^+ is explained in Section 19.6.)
- Phosphate adds to the thioester, forming a tetrahedral intermediate that eliminates the thiolate ion to form the mixed anhydride product. The thiolate ion's leaving propensity is increased by protonation, which makes it a weaker base and, therefore, a better leaving group.

Notice that at the end of the reaction, the enzyme is exactly as it was at the beginning of the reaction, so another molecule of glyceraldehyde-3-phosphate can be converted to 1,3-bisphosphoglycerate.

PROBLEM 10♦

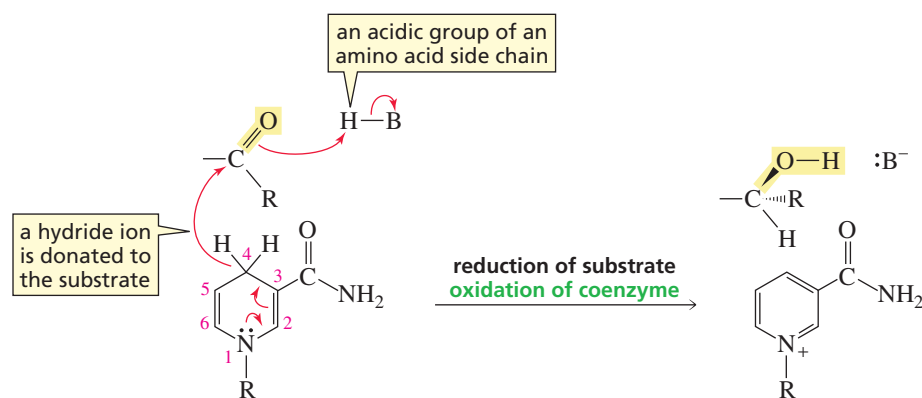
What is the product of the following reaction?

isocitrate + NAD^+ $\xrightarrow{\text{isocitrate dehydrogenase}}$

How Does NADPH Reduce a Substrate?

The mechanism for reduction by NADPH is the reverse of the mechanism for oxidation by NAD^+. When a substrate is being *reduced*, the dihydropyridine ring donates a hydride ion from its 4-position to the substrate. An acidic amino acid side chain of the enzyme aids the reaction by protonating the substrate.

an acidic group of an amino acid side chain

a hydride ion is donated to the substrate

reduction of substrate
oxidation of coenzyme

Because NADPH reduces compounds by donating a hydride ion, it can be considered the biological equivalent of $NaBH_4$ or $LiAlH_4$, the hydride donors we have seen used as reducing reagents in nonbiological reactions (Section 12.7).

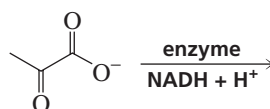
Why are the structures of biological oxidizing and reducing reagents so much more complicated than the structures of the reagents used to carry out the same reactions in the laboratory? NADPH is certainly a more complicated molecule than $NaBH_4$, although both reagents reduce compounds by donating a hydride ion. Much of the structural complexity of a coenzyme is for **molecular recognition**—to allow the coenzyme to be recognized and bound by the enzyme. As you study the coenzymes in this chapter, do not

let the complexity of their structures intimidate you. Notice that only a small part of the coenzyme is actually involved in the chemical reaction.

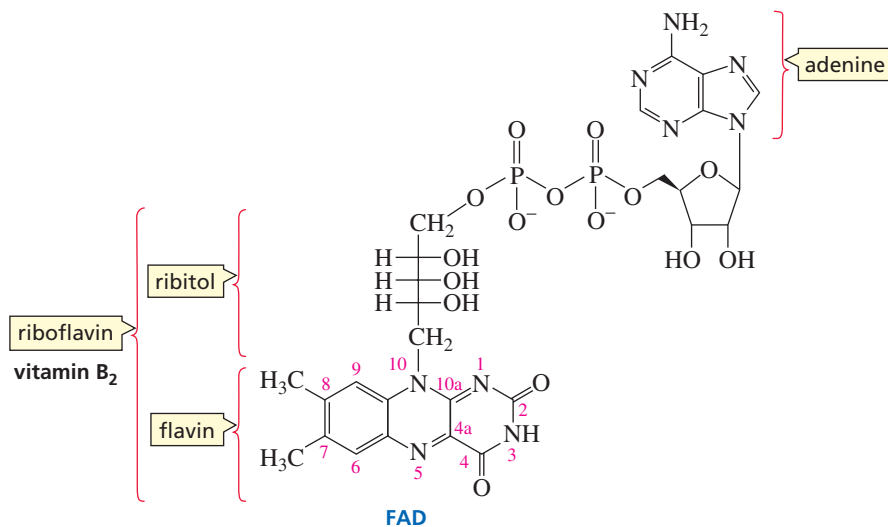
Another reason for the difference in complexity is that reagents used in cells must be highly selective and less reactive than a laboratory reagent. For example, a biological reducing agent cannot reduce just any reducible compound with which it comes into contact. Biological reactions have to be much more carefully controlled than that. Therefore, the coenzymes are relatively unreactive compared with nonbiological reagents: the reaction between the substrate and the coenzyme does not occur at all or takes place very slowly without the enzyme. For example, NADPH will not reduce an aldehyde or a ketone unless an enzyme is present. $NaBH_4$ and $LiAlH_4$ are more reactive hydride donors—in fact, much too reactive to even exist in the aqueous environment of the cell. Similarly, NAD^+ is a much less reactive oxidizing agent than the typical oxidizing agent used in the laboratory—NAD^+ will oxidize an alcohol only in the presence of an enzyme.

PROBLEM 11♦

What is the product of the following reaction?

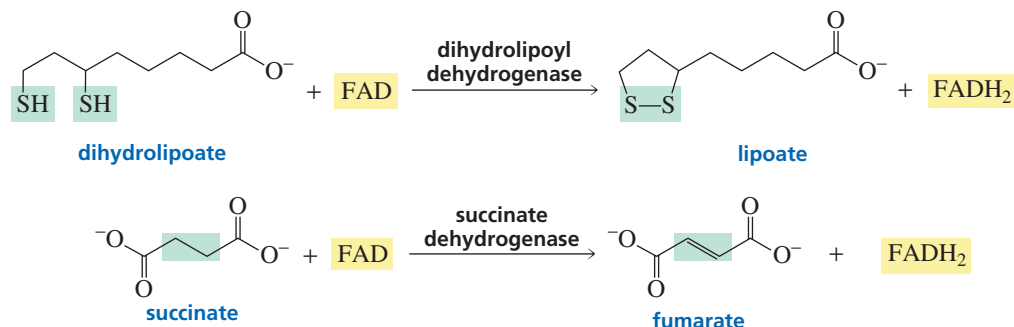
$\xrightarrow[\text{NADH + H}^+]{\text{enzyme}}$

18.8 RIBOFLAVIN: ANOTHER VITAMIN USED IN REDOX REACTIONS

Flavin adenine dinucleotide (FAD), like NAD^+, is a coenzyme used to oxidize a substrate. As its name indicates, FAD is a dinucleotide in which one of the heterocyclic components is flavin and the other is adenine. Notice that instead of ribose, FAD has a reduced ribose (a ribitol group). Flavin plus ribitol is the vitamin known as *riboflavin* or vitamin B_2. Flavin is a bright yellow compound; *flavus* is Latin for "yellow." A vitamin B_2 deficiency causes inflammation of the skin.

adenine
ribitol
riboflavin
vitamin B_2
flavin
FAD

A *flavoprotein* is an enzyme that contains FAD. In most flavoproteins, FAD is bound quite tightly. Tight binding allows the enzyme to control the oxidation potential of the coenzyme. (The more positive the oxidation potential, the stronger is the oxidizing agent.) Consequently, some flavoproteins are stronger oxidizing agents than others.

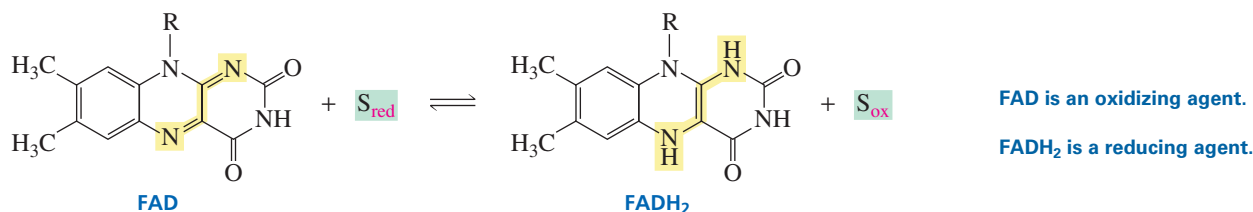
How can we tell which enzymes use FAD and which use NAD^+ as the oxidizing coenzyme? A rough guideline is that NAD^+ is the coenzyme used in enzyme-catalyzed oxidation reactions involving carbonyl compounds, whereas FAD is the coenzyme used in other types of oxidations. For example, in the following reactions, FAD oxidizes a dithiol to a disulfide and a saturated alkyl group to an alkene.

dihydrolipoate + FAD --dihydrolipoyl dehydrogenase--> lipoate + $FADH_2$

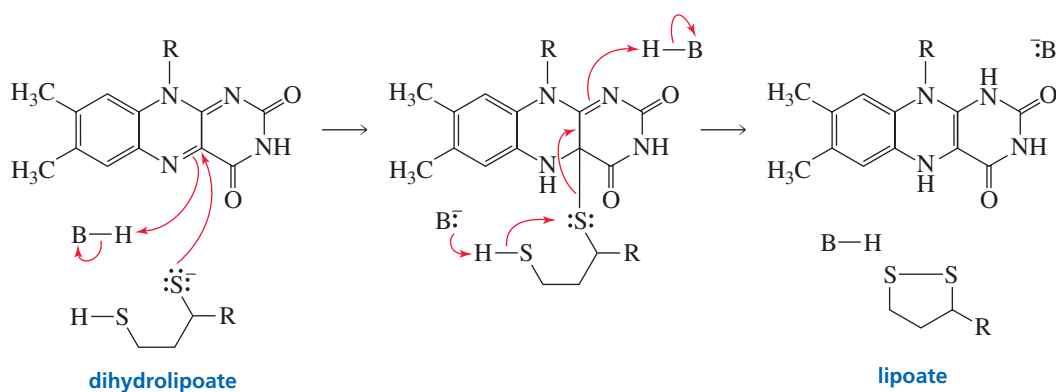
succinate + FAD --succinate dehydrogenase--> fumarate + $FADH_2$

When FAD oxidizes a substrate, the coenzyme is reduced to $FADH_2$. $FADH_2$, like NADPH, is a reducing agent. All the oxidation–reduction chemistry takes place on the flavin ring.

FAD + S_{red} ⇌ $FADH_2$ + S_{ox}

FAD is an oxidizing agent.

$FADH_2$ is a reducing agent.

The mechanism proposed for the FAD-catalyzed oxidation of dihydrolipoate to lipoate is shown here.

MECHANISM PROPOSED FOR THE REACTION CATALYZED BY DIHYDROLIPOYL DEHYDROGENASE

dihydrolipoate → → lipoate

- The thiolate ion adds to the 4a-position of the flavin ring. This is an acid-catalyzed reaction: an amino acid side chain close to the N-5 nitrogen donates a proton to it.
- A second thiolate ion attacks the sulfur that is covalently attached to the coenzyme, forming the oxidized product and $FADH_2$. This is a base-catalyzed reaction: a base removes a proton from the sulfur to make it a better nucleophile.

PROBLEM 12♦

How many conjugated double bonds are there in

a. FAD? **b.** $FADH_2$?

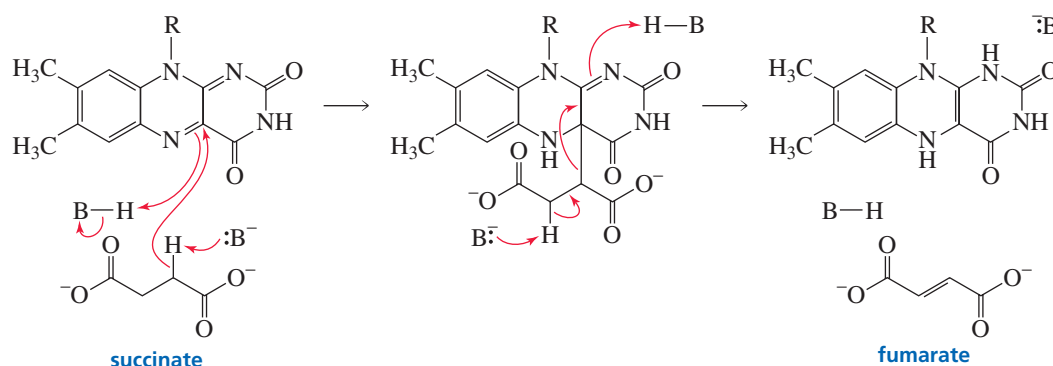
PROBLEM 13♦

Instead of adding to the 4a-position and protonating N-5, the thiolate ion could have added to the 10a-position and protonated N-1. Why is addition to the 4a-position favored? (*Hint:* Which nitrogen is a stronger base?)

The mechanism proposed for the FAD-catalyzed oxidation of succinate to fumarate is similar to the mechanism you have just seen for the FAD-catalyzed oxidation of dihydrolipoate to lipoate.

MECHANISM PROPOSED FOR THE REACTION CATALYZED BY SUCCINATE DEHYDROGENASE

succinate

fumarate

- A base removes a proton from the α-carbon, creating a nucleophile that adds to the 4a-position of the flavin ring. A proton is donated simultaneously to the N-5 nitrogen.
- A base removes a proton from the other α-carbon, forming the oxidized product and $FADH_2$.

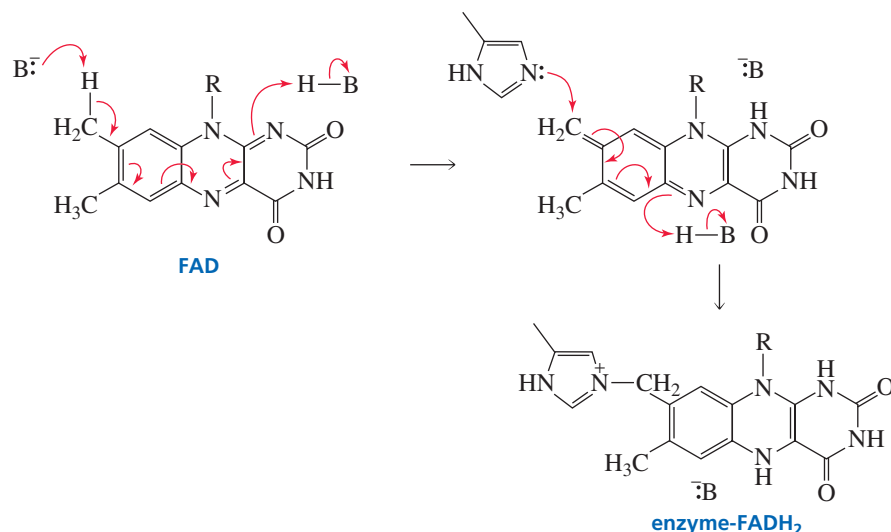
NAD^+ is only loosely bound to its enzyme and, after being reduced to NADH, it dissociates from the enzyme. In contrast, FAD is tightly bound to its enzyme (**E** = enzyme; **S** = substrate). If it remains bound after being reduced to $FADH_2$, it has to be reoxidized to FAD before the enzyme can begin another round of catalysis. The oxidizing agent used for this reaction is NAD^+ or O_2. Therefore, an enzyme that uses an oxidizing coenzyme other than NAD^+ may still require NAD^+ to oxidize the reduced coenzyme.

$$\text{E(FAD)} + \text{S}_{red} \longrightarrow \text{E(FADH}_2\text{)} + \text{S}_{ox} \xrightarrow{\text{NAD}^+ \;\rightarrow\; \text{NADH} + \text{H}^+} \text{E(FAD)}$$

PROBLEM 14 Solved

In succinate dehydrogenase, FAD is covalently bound to its enzyme as a result of a base removing a proton from the C-8 methyl group and an acid donating a proton to N-1. Then, a histidine side chain of the enzyme adds to the methylene carbon at C-8 as a proton adds to N-5. Draw the mechanism for these two steps that lead to enzyme-bound $FADH_2$.

Solution

FAD

enzyme-$FADH_2$

Notice that FAD is reduced to $FADH_2$ during the process of being attached to the enzyme. It is subsequently oxidized back to FAD by NAD^+. Once the coenzyme is covalently attached to the enzyme, it does not come off.

PROBLEM 15

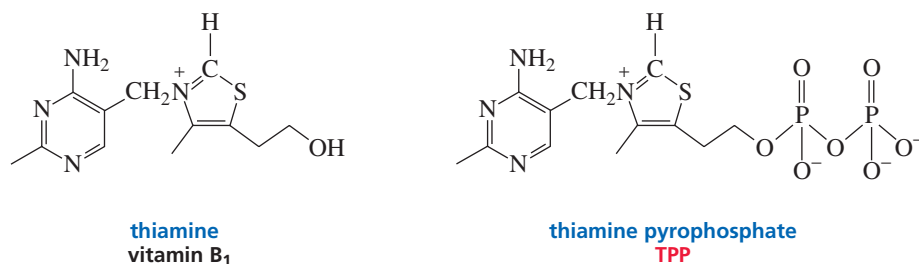
Explain why the hydrogens of the C-8 methyl group are more acidic than those of the C-7 methyl group.

18.9 VITAMIN B_1: THE VITAMIN NEEDED FOR ACYL GROUP TRANSFER

Thiamine was the first of the B vitamins to be identified, so it became known as vitamin B_1. The absence of thiamine in the diet causes a disease called beriberi, which damages the heart, impairs nerve reflexes, and in extreme cases causes paralysis (page 15).

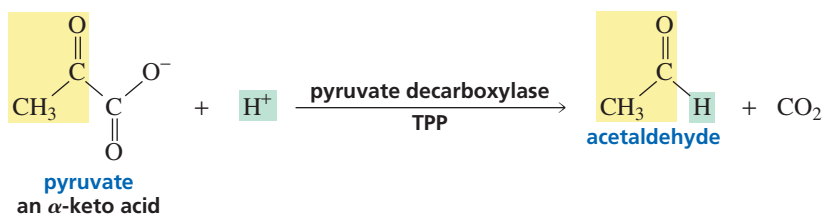
Vitamin B_1 is used to form the coenzyme **thiamine pyrophosphate (TPP).** TPP is the coenzyme required by enzymes that catalyze the transfer of an acyl group from one group to another.

thiamine
vitamin B_1

thiamine pyrophosphate
TPP

Pyruvate decarboxylase is an enzyme that requires thiamine pyrophosphate. This enzyme catalyzes the decarboxylation of pyruvate and transfers the remaining acyl group to a proton, resulting in the formation of acetaldehyde. A *decarboxylase* is an enzyme that catalyzes the removal of CO_2 from a substrate.

pyruvate + H^+ —(pyruvate decarboxylase, TPP)→ acetaldehyde + CO_2

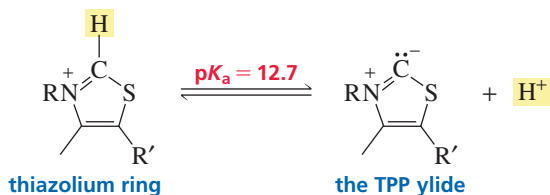
pyruvate
an α-keto acid

acetaldehyde

Thiamine pyrophosphate (TPP) is required by enzymes that catalyze the transfer of an acyl group from one group to another.

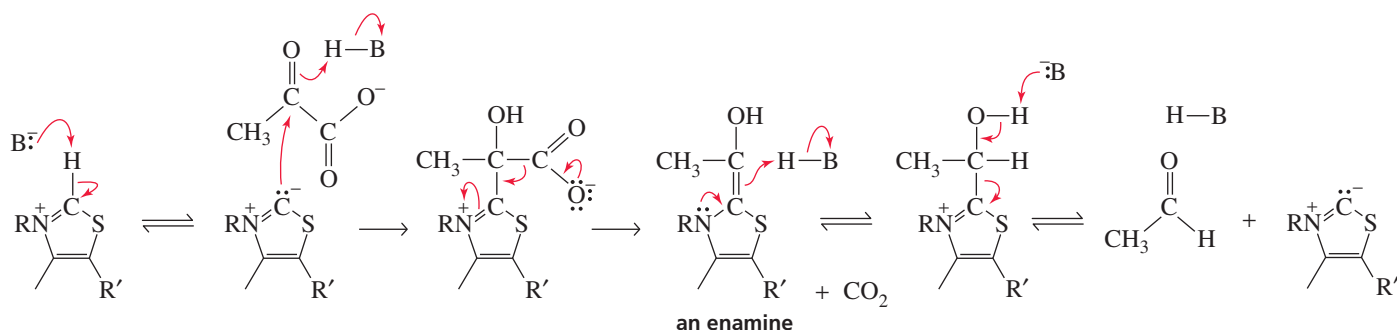
You may be wondering how an α-keto acid such as pyruvate can be decarboxylated, since the electrons left behind when CO_2 is removed cannot be delocalized onto the carbonyl oxygen. We will see that the thiazolium ring of the coenzyme provides a site to which the electrons can be delocalized.

The hydrogen bonded to the imine carbon of TPP is relatively acidic (pK_a = 12.7) compared to a hydrogen attached to other sp^2 carbons, because the TPP ylide formed when the proton is removed is stabilized by the adjacent positively charged nitrogen. The TPP ylide is a good nucleophile.

pKa = 12.7

thiazolium ring

the TPP ylide

MECHANISM FOR THE REACTION CATALYZED BY PYRUVATE DECARBOXYLASE

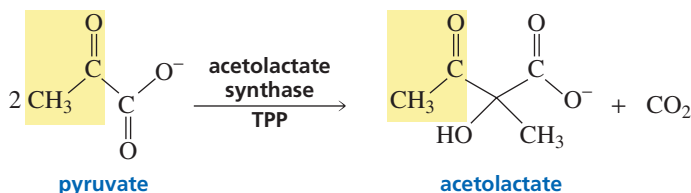
an enamine

- After the proton is removed, the TPP ylide adds to the carbonyl carbon of the α-keto acid. An acid side chain of the enzyme increases the electrophilicity of the carbonyl carbon.
- The tetrahedral intermediate thus formed can easily undergo decarboxylation because the electrons left behind when CO_2 is removed can be delocalized onto the positively charged nitrogen. The decarboxylated product is an enamine. (An enamine is a tertiary amine that has its nitrogen atom attached to an sp^2 carbon.)
- Protonation of the enamine on carbon and a subsequent base-catalyzed elimination reaction forms acetaldehyde and regenerates the TPP ylide.

A site to which electrons can be delocalized is called an **electron sink.** The positively charged nitrogen of TPP is a more effective electron sink than the β-keto group of a β-keto acid, a class of compounds that we have seen are fairly easily decarboxylated (Section 13.9).

PROBLEM 16

Acetolactate synthase is another TPP-requiring enzyme. It, too, catalyzes the decarboxylation of pyruvate, but it transfers the resulting acyl group to another molecule of pyruvate, forming acetolactate. This is the first step in the biosynthesis of the amino acids valine and leucine. Propose a mechanism for this reaction.

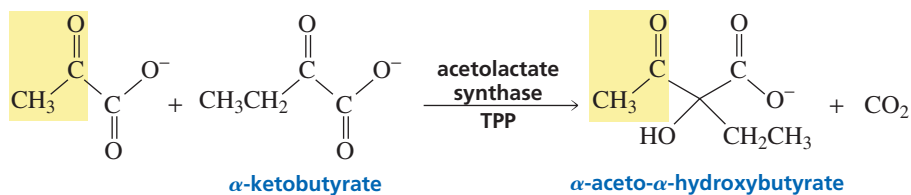
acetolactate synthase
TPP

pyruvate

acetolactate

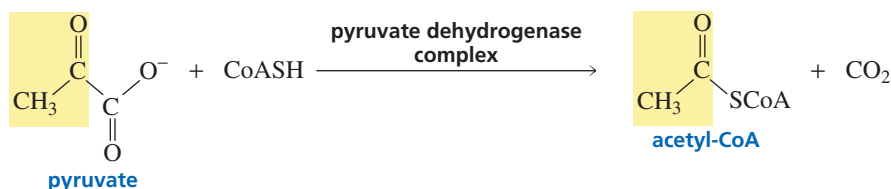
PROBLEM 17

Acetolactate synthase can also transfer the acyl group from pyruvate to α-ketobutyrate. This is the first step in the formation of the amino acid isoleucine. Propose a mechanism for this reaction.

$$CH_3COCOO^- + CH_3CH_2COCOO^- \xrightarrow[\text{TPP}]{\text{acetolactate synthase}} CH_3CO{-}C(OH)(CH_2CH_3){-}COO^- + CO_2$$

α-ketobutyrate → α-aceto-α-hydroxybutyrate

We will see in Chapter 19 that the final product of carbohydrate metabolism is pyruvate. For pyruvate to be further metabolized, it must be converted to acetyl-CoA. The *pyruvate dehydrogenase complex* is a group of three enzymes responsible for transferring the acyl group of pyruvate to CoASH in order to form acetyl-CoA.

$$CH_3COCOO^- + \text{CoASH} \xrightarrow{\text{pyruvate dehydrogenase complex}} CH_3COSCoA + CO_2$$

pyruvate → acetyl-CoA

The pyruvate dehydrogenase complex requires TPP and four other coenzymes: lipoate, coenzyme A, FAD, and NAD^+.

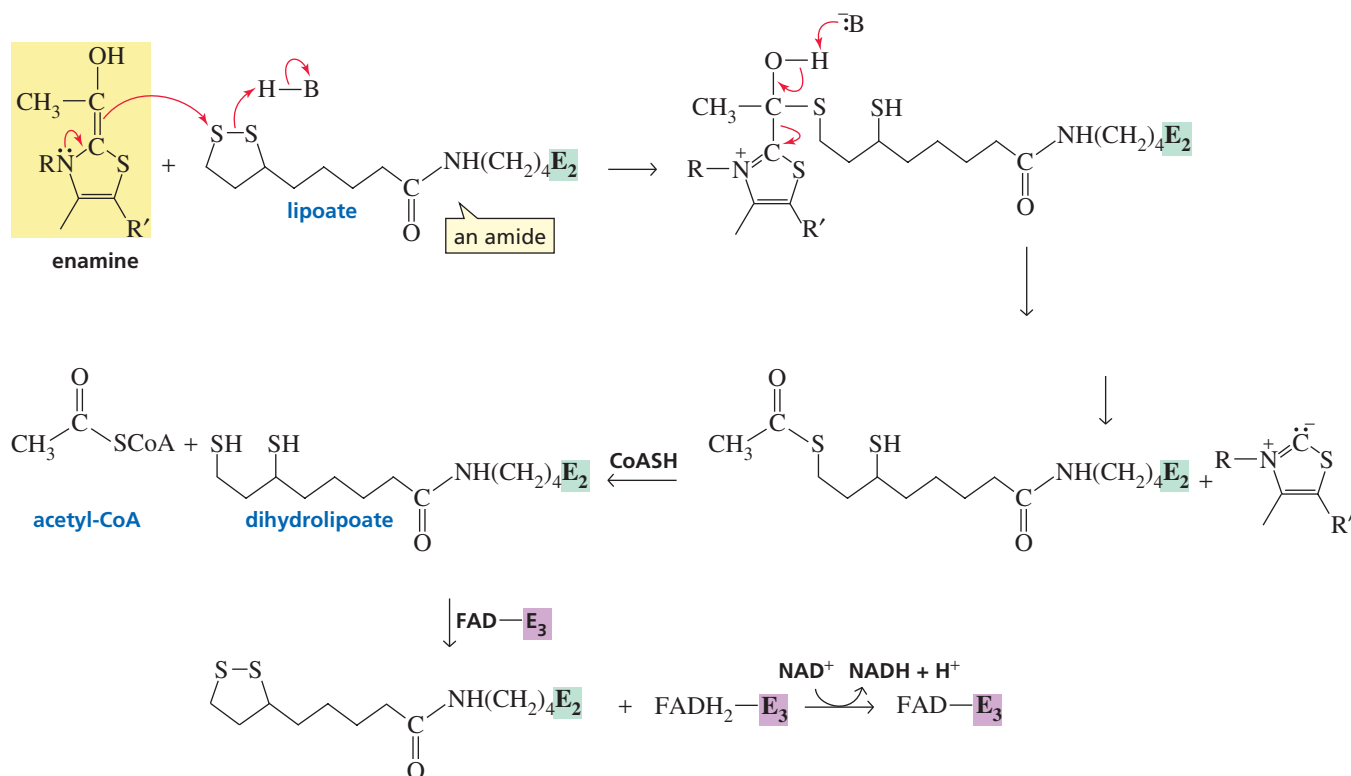
MECHANISM FOR THE REACTION CATALYZED BY THE PYRUVATE DEHYDROGENASE COMPLEX

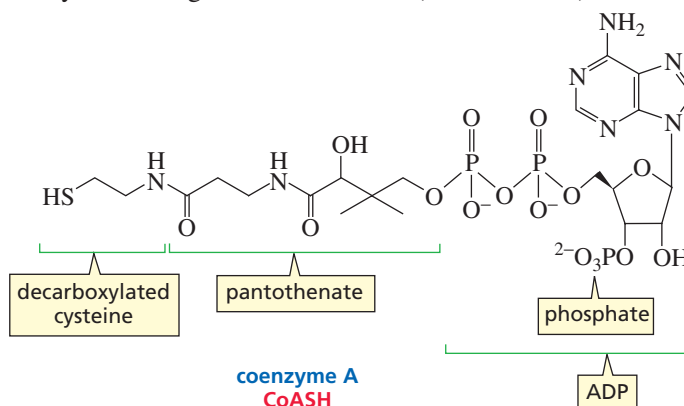
enamine + lipoate ($NH(CH_2)_4E_2$; an amide; H—B) → CH_3—C(OH)(S-lipoyl)—thiazolium intermediate (:B⁻)

→ acetyl-dihydrolipoyl-$NH(CH_2)_4E_2$ + ylide (R—N⁺=C̈⁻—S, R′)

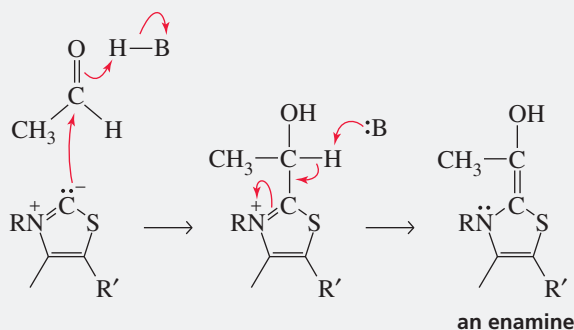
$\xrightarrow{\text{CoASH}}$ acetyl-CoA + dihydrolipoate ($NH(CH_2)_4E_2$)

$\downarrow$ FAD—E_3

lipoate ($NH(CH_2)_4E_2$) + $FADH_2$—E_3 $\xrightarrow{NAD^+ \;\; NADH + H^+}$ FAD—E_3

- The first enzyme in the complex (the reaction is shown on page 24) catalyzes the reaction of the TPP ylide with pyruvate to form the same enamine that is formed by pyruvate decarboxylase and by the enzyme in Problems 16 and 17.
- The second enzyme of the complex (**E_2**) uses a lysine side chain to form an amide with its coenzyme (**lipoate**). The disulfide bond of lipoate is broken when it undergoes nucleophilic attack by the enamine.
- The TPP ylide is eliminated from the tetrahedral intermediate.
- **Coenzyme A (CoASH)** reacts with the thioester in a transthioesterification reaction (one thioester is converted to another), substituting coenzyme A for dihydrolipoate (Section 11.7). At this point, the final reaction product (acetyl-CoA) has been formed.
- Before another catalytic cycle can occur, dihydrolipoate must be oxidized back to lipoate. This is done by the third enzyme (**E_3**), an FAD-requiring enzyme. We saw the mechanism for this reaction in Section 18.8. When dihydrolipoate is oxidized by FAD, the coenzyme is reduced to $FADH_2$.
- NAD^+ oxidizes $FADH_2$ back to FAD.

The vitamin needed to make coenzyme A is pantothenate. In coenzyme A, pantothenate is attached to a decarboxylated cysteine (recall that cysteine is an amino acid) and a phosphorylated ADP. We have seen that CoASH is used in biological systems to activate carboxylic acids by converting them to thioesters (Section 11.16).

Curing a Hangover with Vitamin B_1

An unfortunate effect of drinking too much alcohol, known as a hangover, is attributable to the acetaldehyde formed when ethanol is oxidized (Section 9.5). A common belief is that vitamin B_1 can cure a hangover by getting rid of acetaldehyde. Let's see how the vitamin is able to do this.

The TPP ylide adds to the carbonyl carbon of the acetaldehyde. Removal of a proton forms the same enamine that is formed by both pyruvate decarboxylase and the pyruvate dehydrogenase complex—the only difference in the reactions is that a proton, instead of a carboxyl group, is removed from the substrate. The enamine then reacts with lipoate just as it does in the pyruvate dehydrogenase complex. The result is that the offending acetaldehyde is converted to acetyl-CoA.

There is a limit to the amount of acetaldehyde that can be converted to acetyl-CoA in a given amount of time, so the vitamin can cure only hangovers that result from moderate drinking.

PROBLEM 18

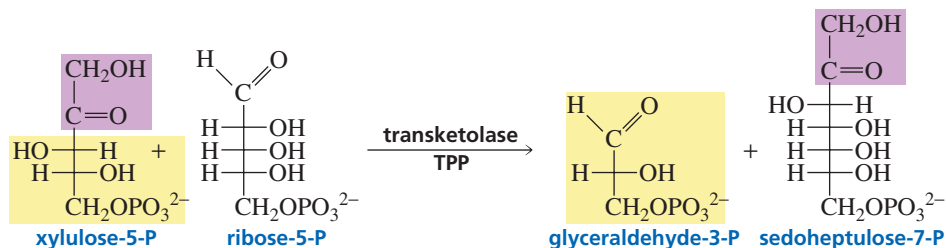
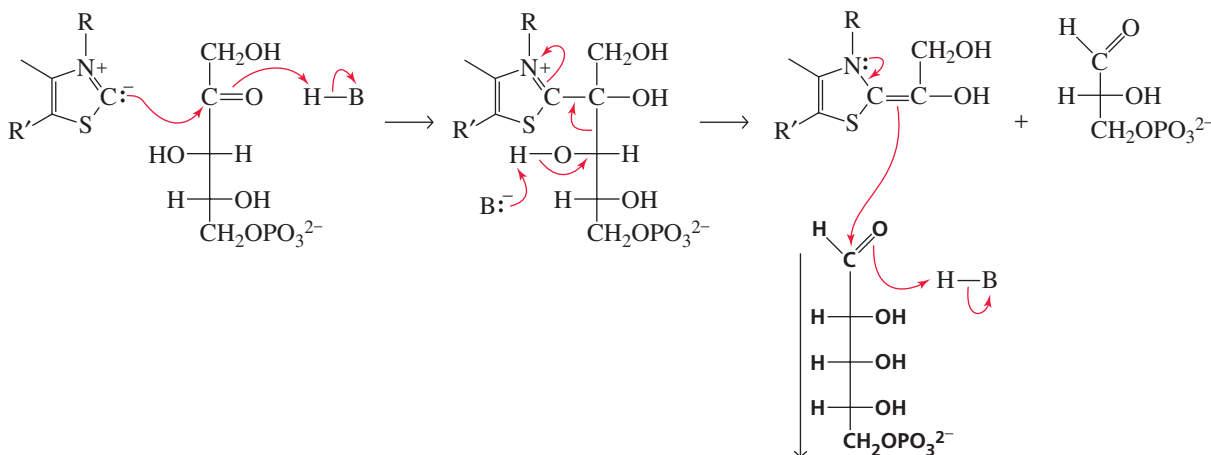
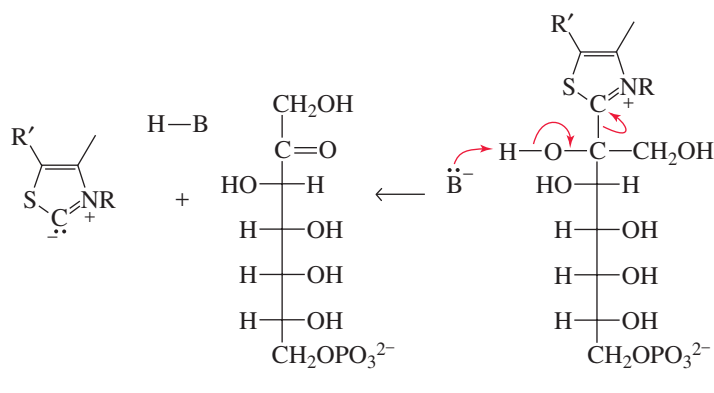
Draw structures that show the similarity between the decarboxylation of the pyruvate–TPP intermediate and the decarboxylation of a β-keto acid.

PROBLEM 19♦

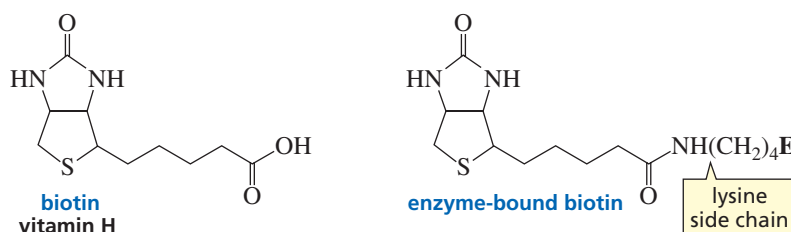
a. What two-carbon fragment does pyruvate decarboxylase transfer to a proton?
b. What two-carbon fragment does the pyruvate dehydrogenase complex transfer to coenzyme A?

PROBLEM 20 Solved

TPP is a coenzyme for transketolase, the enzyme that catalyzes the conversion of a ketopentose (xylulose-5-phosphate) and an aldopentose (ribose-5-phosphate) into an aldotriose (glyceraldehyde-3-phosphate) and a ketoheptose (sedoheptulose-7-phosphate). Notice that the total number of carbons in the reactants and products is the same (5 + 5 = 3 + 7). Propose a mechanism for this reaction.

xylulose-5-P + ribose-5-P $\xrightarrow[\text{TPP}]{\text{transketolase}}$ glyceraldehyde-3-P + sedoheptulose-7-P

Solution The reaction shows that an acyl group (purple box) is transferred from xylulose-5-phosphate to ribose-5-phosphate. Because the enzyme requires TPP, we know that TPP must be the species that removes and transfers the acyl group. Thus, the reaction must start by the addition of the TPP ylide to the carbonyl group of xylulose-5-phosphate. We can add an acid group to accept the electrons from the carbonyl group and a basic group to help form the enamine. Notice that, like in other TPP-catalyzed reactions, the electrons left behind by the group that is removed from the acyl group are delocalized onto the nitrogen of the thiazolium ring. The enamine then transfers the acyl group to the carbonyl carbon of ribose-5-phosphate. Again, an acid group accepts the electrons from the carbonyl group, and a basic group helps eliminate the TPP ylide.

Notice the similar function of TPP in all TPP-requiring enzymes. In each reaction, the TPP ylide adds to a carbonyl carbon of the substrate and allows a bond to that carbon to be broken because the electrons left behind can be delocalized onto the nitrogen atom of the thiazolium ring. The acyl group is then transferred—to a proton in the case of pyruvate decarboxylase, to coenzyme A (via lipoate) in the pyruvate dehydrogenase system, and to a carbonyl group in Problems 16, 17, and 20.

18.10 VITAMIN H: THE VITAMIN NEEDED FOR CARBOXYLATION OF AN α-CARBON

Biotin (vitamin H) is an unusual vitamin because it is synthesized by bacteria that live in the intestine. Consequently, biotin does not have to be included in our diet, and deficiencies are rare. Biotin deficiencies, however, can be found in people who maintain a diet high in raw eggs. Egg whites contain a protein (called avidin) that binds biotin tightly and thereby prevents it from acting as a coenzyme. When eggs are cooked, avidin is denatured, and the denatured protein does not bind biotin. Biotin, like lipoic acid, is attached to its enzyme (**E**) by forming an amide with the amino group of a lysine side chain.

biotin
vitamin H

enzyme-bound biotin

lysine side chain

Biotin is the coenzyme required by enzymes that catalyze the carboxylation of an α-carbon (a carbon adjacent to a carbonyl group). Therefore, the enzymes that require biotin as a coenzyme are called carboxylases.

Biotin is required by enzymes that catalyze the carboxylation of an α-carbon.

For example, pyruvate carboxylase converts pyruvate to oxaloacetate, and acetyl-CoA carboxylase converts acetyl-CoA to malonyl-CoA. Biotin-requiring enzymes use bicarbonate (HCO_3^-) for the source of the carboxyl group that becomes attached to the α-carbon of the substrate.

pyruvate + HCO_3^- + ATP —(pyruvate carboxylase, Mg^{2+}, biotin)→ oxaloacetate + ADP + HPO_4^{2-}

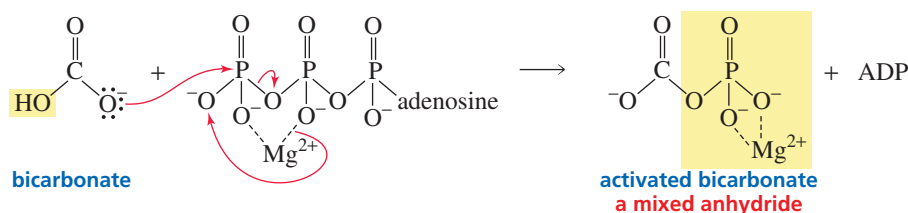
a carboxyl group has been added to the α-carbon

$CH_3C(=O)SCoA$ (acetyl-CoA) + HCO_3^- + ATP $\xrightarrow[\text{Mg}^{2+},\ \text{biotin}]{\text{acetyl-CoA carboxylase}}$ $^-OOC{-}CH_2C(=O)SCoA$ (malonyl-CoA) + ADP + $HOPO_3^{2-}$

a carboxyl group has been added to the α-carbon

In addition to bicarbonate, biotin-requiring enzymes also require ATP and Mg^{2+}. The function of Mg^{2+} is to decrease the overall negative charge on ATP by complexing with two of its negatively charged oxygens. Unless its negative charge is reduced, ATP cannot be approached by a nucleophile (see Figure 11.2).

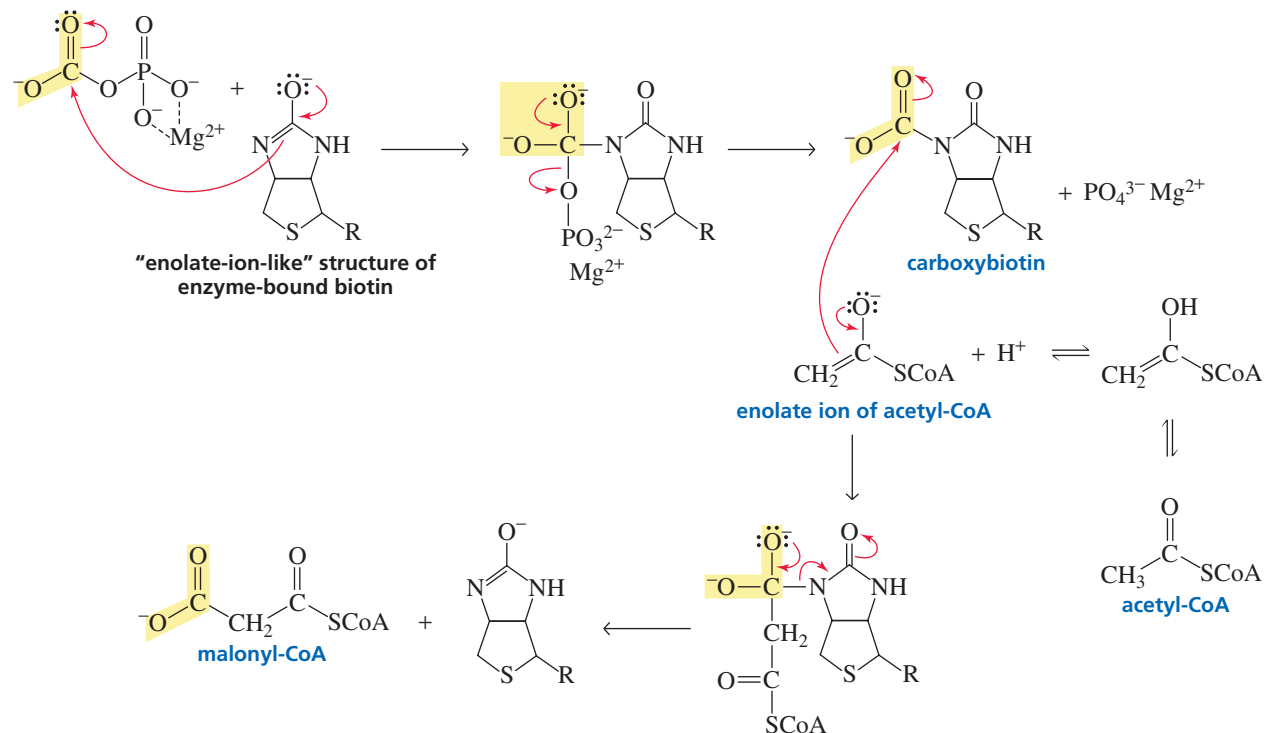
The function of ATP is to increase the reactivity of bicarbonate by converting it to "activated bicarbonate"—a compound with a good leaving group. To form "activated bicarbonate," bicarbonate attacks the γ-phosphorus of ATP and expels ADP (Section 11.16). Notice that "activated bicarbonate" is a mixed anhydride of carbonic acid and phosphoric acid.

bicarbonate + ATP (Mg^{2+}) ⟶ activated bicarbonate (a mixed anhydride) + ADP

Once bicarbonate has been activated, the catalytic reaction can begin. The mechanism for the carboxylation of acetyl CoA is shown next.

MECHANISM FOR THE REACTION CATALYZED BY ACETYL-CoA CARBOXYLASE

activated bicarbonate (Mg^{2+}) + "enolate-ion-like" structure of enzyme-bound biotin ⟶ tetrahedral intermediate (PO_3^{2-}, Mg^{2+}) ⟶ carboxybiotin + PO_4^{3-} Mg^{2+}

acetyl-CoA ⇌ $CH_2{=}C(OH)SCoA$ ⇌ enolate ion of acetyl-CoA + H^+

enolate ion of acetyl-CoA + carboxybiotin ⟶ tetrahedral intermediate ⟶ malonyl-CoA + biotin

- Biotin reacts with activated bicarbonate in a nucleophilic acyl substitution reaction to form carboxybiotin. Because the nitrogen of an amide is not nucleophilic, the active form of biotin has an enolate-ion-like structure. (Section 13.3)
- The substrate (in this case, the enolate ion of acetyl-CoA) reacts with carboxybiotin in a second nucleophilic acyl substitution reaction that transfers the carboxyl group from carboxybiotin to the substrate.

All biotin-requiring enzymes follow the same three steps: activation of bicarbonate by ATP, reaction of activated bicarbonate with biotin to form carboxybiotin, and transfer of the carboxyl group from carboxybiotin to the substrate.

PROBLEM-SOLVING STRATEGY

How many moles of acetyl-CoA must be converted to malonyl-CoA in order to synthesize 1 mole of palmitic acid, a 16-carbon saturated fatty acid?

To answer this question, we need to recall how fatty acids are biosynthesized (Section 13.10). The biosynthesis starts with the reaction of a molecule of acetyl thioester and a molecule of malonyl thioester to form a four-carbon fatty acid. Each subsequent two-carbon unit is added by a molecule of malonyl thioester. Twelve more carbons are needed to form palmitic acid, so another six molecules of malonyl-CoA are required. Therefore, the synthesis of palmitic acid requires 7 moles of acetyl-CoA to be converted to malonyl-CoA.

Now continue on to Problem 21.

PROBLEM 21♦

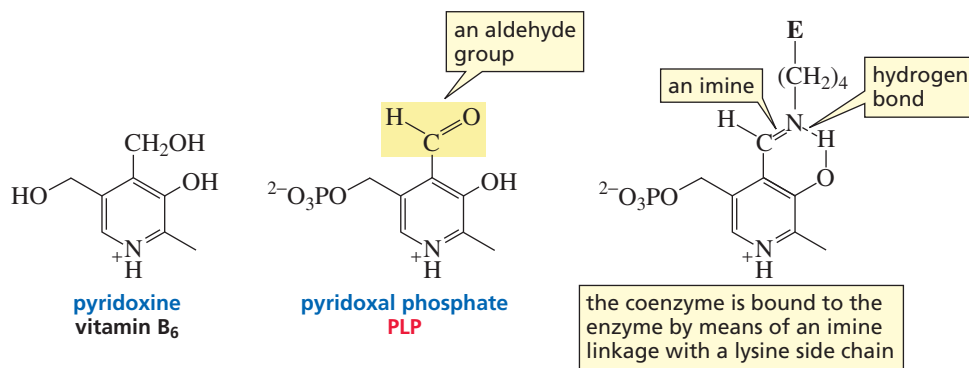
How many moles of acetyl-CoA must be converted to malonyl-CoA in order to synthesize 1 mole of arachidic acid, a 20-carbon saturated fatty acid?

PROBLEM 22 Solved

How many moles of ATP are needed to make 1 mole of palmitic acid?

Solution One mole of a 16-carbon fatty acid is synthesized from 1 mole of acetyl-CoA and 7 moles of malonyl-CoA. Each mole of malonyl-CoA synthesized from acetyl-CoA requires 1 mole of ATP (for the carboxylation reaction). Therefore, 7 moles of ATP are needed to make 1 mole of palmitic acid.

18.11 VITAMIN B_6: THE VITAMIN NEEDED FOR AMINO ACID TRANSFORMATIONS

The coenzyme **pyridoxal phosphate (PLP)** is derived from vitamin B_6, which is also known as pyridoxine. (Pyridoxal's "al" suffix indicates that the coenzyme is an aldehyde.) A deficiency in vitamin B_6 causes anemia; severe deficiencies can cause seizures and death.

an aldehyde group

an imine

hydrogen bond

pyridoxine
vitamin B_6

pyridoxal phosphate
PLP

the coenzyme is bound to the enzyme by means of an imine linkage with a lysine side chain

PLP is required by enzymes that catalyze certain reactions of amino acids, such as decarboxylation, transamination, and racemization.

decarboxylation

$$\text{R}\text{CH}(\overset{+}{\text{N}}\text{H}_3)\text{COO}^- \xrightarrow[\text{PLP}]{\text{E}} \text{RCH}_2\overset{+}{\text{N}}\text{H}_3 + \text{CO}_2$$

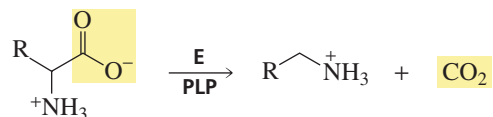
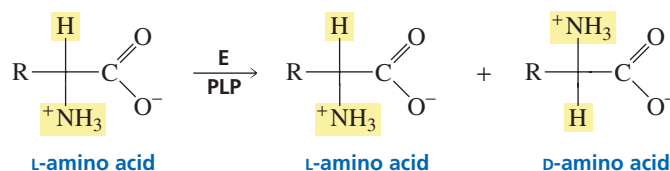
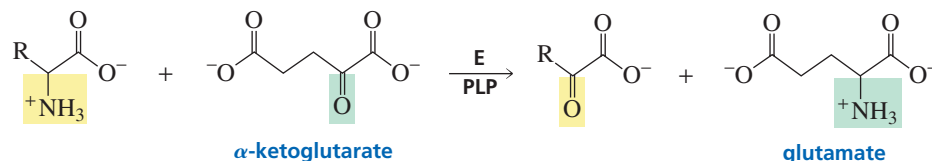
racemization

$$\text{L-amino acid} \xrightarrow[\text{PLP}]{\text{E}} \text{L-amino acid} + \text{D-amino acid}$$

L-amino acid L-amino acid D-amino acid

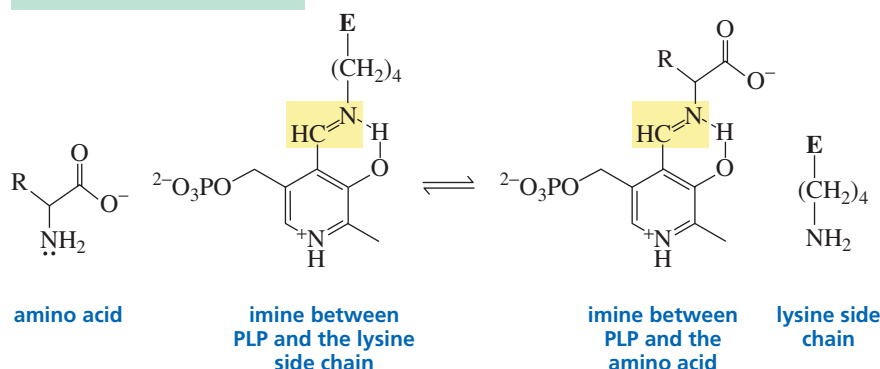
transamination

$$\text{amino acid} + \alpha\text{-ketoglutarate} \xrightarrow[\text{PLP}]{\text{E}} \alpha\text{-keto acid} + \text{glutamate}$$

α-ketoglutarate glutamate

Pyridoxal phosphate (PLP) is required by enzymes that catalyze certain reactions of amino acids.

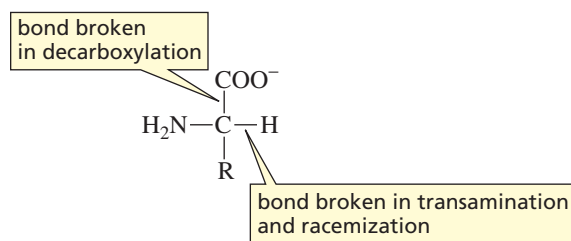
PLP becomes attached to its enzyme by forming an imine with the amino group of a lysine side chain. The first step in all reactions catalyzed by PLP-requiring enzymes is a **transimination** reaction—a reaction that converts one imine into another imine. Thus, the amino acid substrate reacts with the imine formed by PLP and the lysine side chain, and forms an imine with PLP and releases the lysine side chain.

a transimination reaction

amino acid + imine between PLP and the lysine side chain ⇌ imine between PLP and the amino acid + lysine side chain

Once the amino acid has formed an imine with PLP, the next step is to break a bond to the α-carbon of the amino acid. Decarboxylation breaks the bond joining the carboxyl group to the α-carbon; transamination and racemization break the bond joining the hydrogen to the α-carbon.

bond broken in decarboxylation

$$H_2N-\underset{R}{\overset{COO^-}{C}}-H$$

bond broken in transamination and racemization

A bond to the α-carbon can be broken because the electrons left behind when the bond breaks can be delocalized onto the positively charged nitrogen of the protonated pyridine (pyridinium) ring. Thus, the protonated nitrogen is an electron sink. The coenzyme loses much of its activity if the OH group is removed from the pyridinium ring. Apparently, the hydrogen bond formed by the OH group helps weaken the bond to the α-carbon.

Decarboxylation

All enzymes that catalyze the decarboxylation of an amino acid do so by the mechanism shown here.

MECHANISM FOR THE PLP-CATALYZED DECARBOXYLATION OF AN AMINO ACID

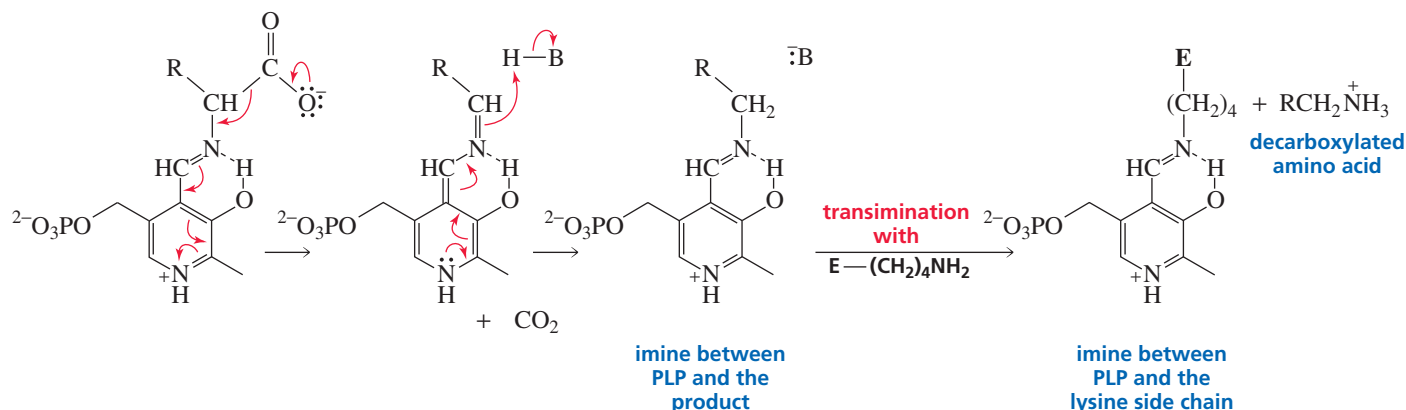
$+\ CO_2$

transimination with $E{-}(CH_2)_4NH_2$

$+\ RCH_2\overset{+}{N}H_3$

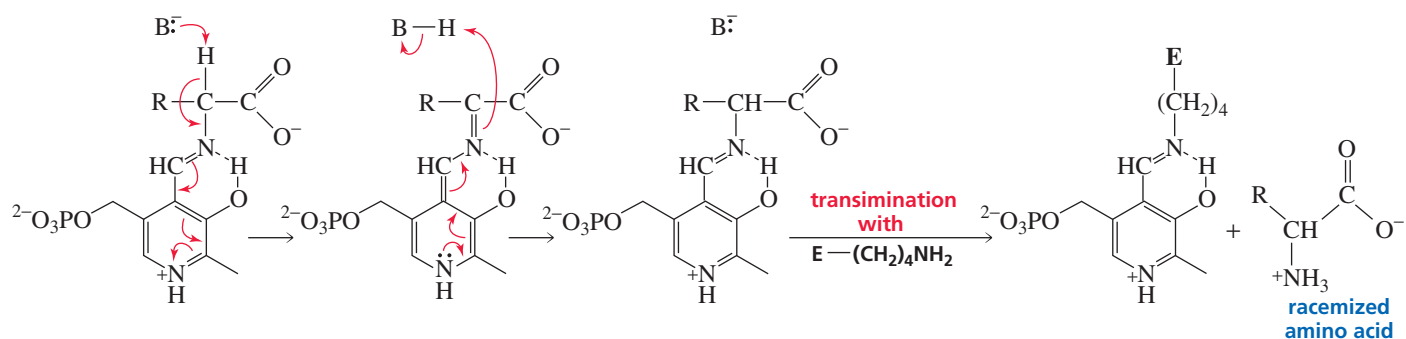
decarboxylated amino acid

imine between PLP and the product

imine between PLP and the lysine side chain

- The carboxyl group is removed from the α-carbon in the first step; the electrons left behind are delocalized onto the positively charged nitrogen.
- The aromaticity of the pyridinium ring is reestablished by electron rearrangement and protonation of what was the α-carbon of the amino acid.
- The last step in all PLP-requiring enzymes is another transimination reaction. The imine formed by PLP and the product of the enzyme-catalyzed reaction reacts with the lysine side chain of the enzyme, forming an imine with PLP and releasing the product.

Racemization

The mechanism for the PLP-catalyzed racemization of an L-amino acid is shown next. Notice that the mechanism for the interconversion of the enantiomers is the same as the mechanism for decarboxylation except for the group removed from the α-carbon of the amino acid in the first step.

MECHANISM FOR THE PLP-CATALYZED RACEMIZATION OF AN L-AMINO ACID

transimination with $E{-}(CH_2)_4NH_2$

racemized amino acid

- A proton is removed from the α-carbon, and the electrons left behind are delocalized onto the positively charged nitrogen.
- The aromaticity of the pyridinium ring is reestablished by electron rearrangement and protonation of what was the α-carbon of the amino acid.
- A transimination reaction with a lysine side chain releases the product of the reaction (the racemized amino acid) and regenerates the imine between the enzyme and PLP.

In the second step of the reaction, the proton can be donated to the sp^2 carbon from either side of the plane defined by the double bond. Consequently, both D- and L-amino acids are formed. In other words, the L-amino acid is racemized.

Transamination

The first reaction in the catabolism of most amino acids is replacement of the amino group of the amino acid by a ketone group. This is called a **transamination** reaction because the amino group removed from the amino acid is not lost, but is *transferred* to the ketone group of α-ketoglutarate, thereby forming glutamate.

The enzymes that catalyze transamination reactions are called *aminotransferases*. Each amino acid has its own aminotransferase. Transamination allows the amino groups of the various amino acids to be collected into a single amino acid (glutamate) so that excess nitrogen can be easily excreted. (Do not confuse *transamination* with *transimination*, discussed previously.)

MECHANISM FOR THE PLP-CATALYZED TRANSAMINATION OF AN AMINO ACID

H_2O

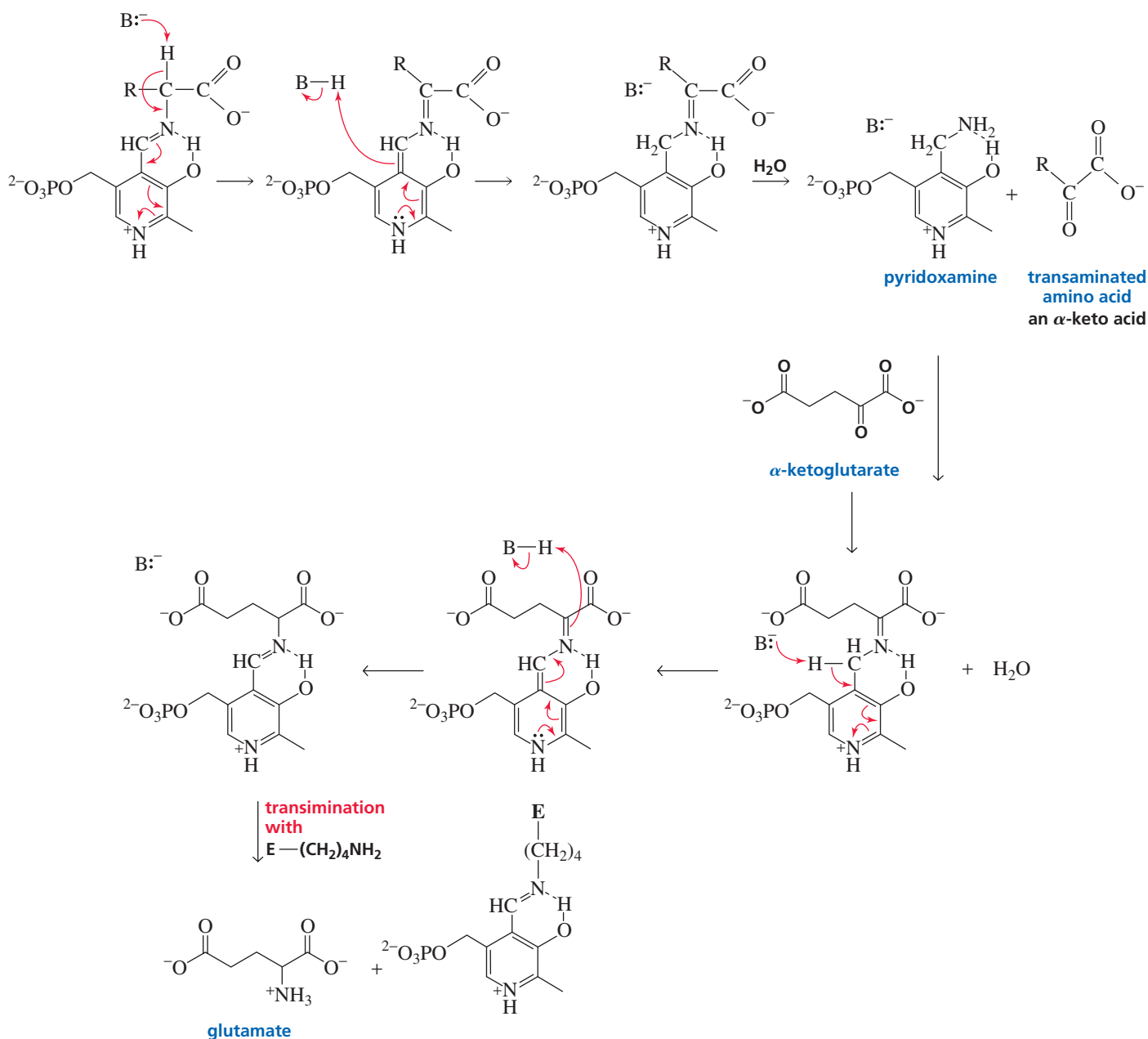
pyridoxamine

transaminated amino acid
an α-keto acid

α-ketoglutarate

+ H_2O

transimination with $E—(CH_2)_4NH_2$

glutamate

- In the first step, a proton is removed from the α-carbon and the electrons left behind are delocalized onto the positively charged nitrogen.
- The aromaticity of the pyridinium ring is reestablished by electron rearrangement and protonation of the carbon attached to the pyridine ring.

- Hydrolysis of the imine forms the transaminated amino acid (an α-keto acid) and pyridoxamine.

At this point, the amino group has been removed from the amino acid, but the amino group of pyridoxamine has to be converted to a carbonyl group that can form an imine with the lysine side chain of the enzyme before another round of catalysis can occur.

- Pyridoxamine forms an imine with α-ketoglutarate, the second substrate of the reaction.
- A proton is removed from the carbon attached to the pyridinium ring and the electrons left behind are delocalized onto the positively charged nitrogen.
- The aromaticity of the pyridinium ring is reestablished by electron rearrangement and protonation of the α-carbon.
- A transimination reaction with a lysine side chain releases the product of the reaction (glutamate) and regenerates the imine between PLP and the lysine side chain of the enzyme.

Notice that the two proton transfer steps are reversed in the two phases of the reaction. Transfer of the amino group of the amino acid to PLP requires removal of the proton from the α-carbon (of the amino acid) and donation of a proton to the carbon bonded to the pyridinium ring. The steps are reversed in the transfer of the amino group of pyridoxamine to α-ketoglutarate: a proton is removed from the carbon bonded to the pyridinium ring, and a proton is donated to the α-carbon (of α-ketoglutarate).

Compare the second step in a PLP-catalyzed transamination with the second step in a PLP-catalyzed decarboxylation or racemization. In an enzyme that catalyzes transamination, an acidic group at the active site is in position to donate a proton to the carbon attached to the pyridinium ring. The enzyme that catalyzes decarboxylation or racemization does not have this acidic group, so the substrate is reprotonated at the α-carbon. In other words, the *coenzyme* carries out the chemical reaction, but the *enzyme* determines the course of the reaction.

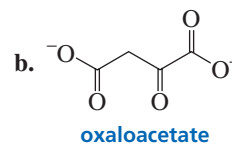
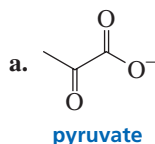
Assessing the Damage After a Heart Attack

After a heart attack, aminotransferases and other enzymes leak from the damaged cells of the heart into the bloodstream. The severity of damage done to the heart can be determined from the concentrations of alanine aminotransferase and aspartate aminotransferase in the blood.

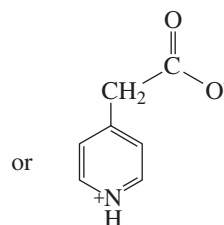
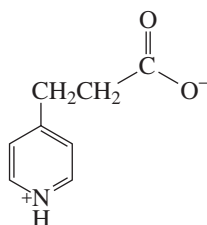
PROBLEM 23♦

α-Keto acids other than α-ketoglutarate can accept the amino group from pyridoxamine in enzyme-catalyzed transamination reactions. What amino acids are formed when the following α-keto acids accept the amino group?

a. pyruvate

b. oxaloacetate

PROBLEM 24♦

Which compound is more easily decarboxylated?

$CH_2CH_2COO^-$ (4-pyridinium, N–H) or CH_2COO^- (4-pyridinium, N–H)

PROBLEM 25♦

Explain why the ability of PLP to catalyze an amino acid transformation is greatly reduced if a PLP-requiring enzymatic reaction is carried out at a pH at which the pyridine nitrogen is not protonated.

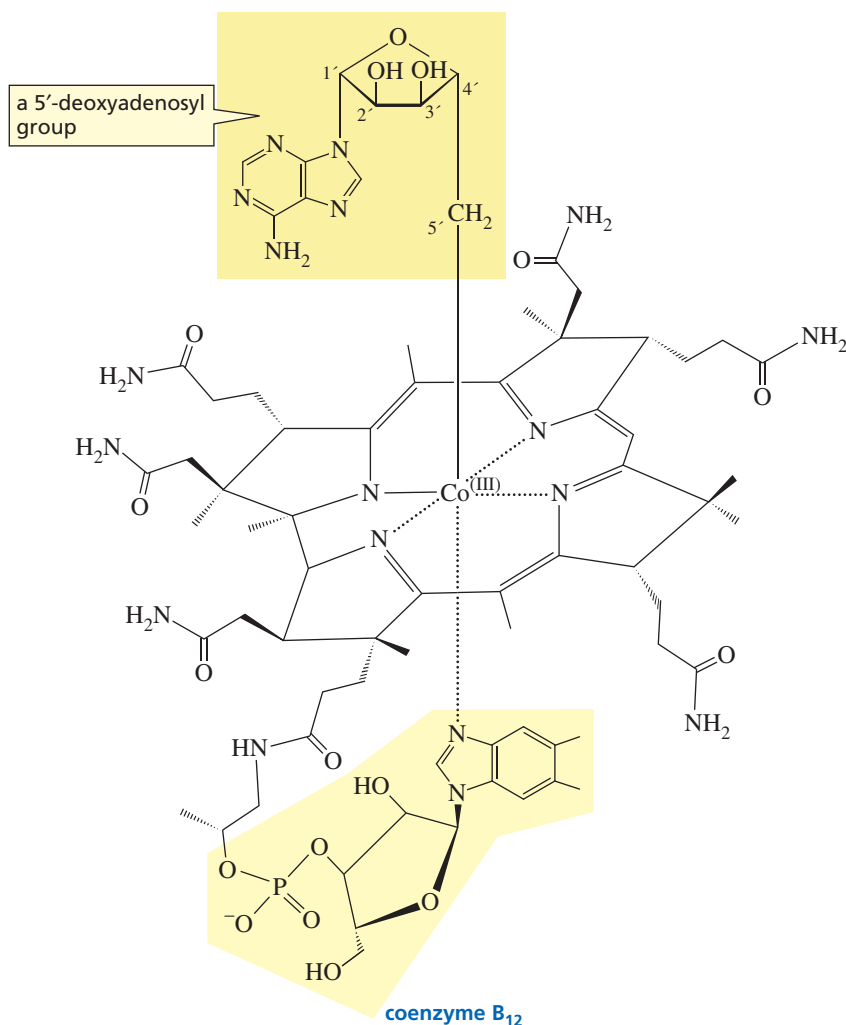
PROBLEM 26♦

Explain why the ability of PLP to catalyze an amino acid transformation is greatly reduced if the OH substituent of PLP is replaced by OCH_3.

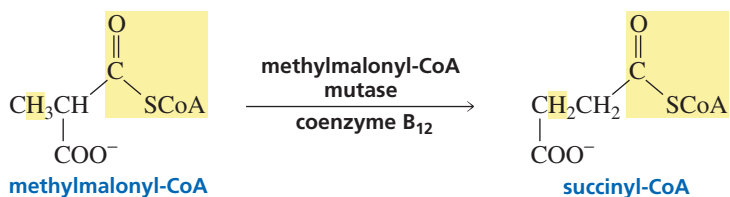
18.12 VITAMIN B_{12}: THE VITAMIN NEEDED FOR CERTAIN ISOMERIZATIONS

Enzymes that catalyze certain isomerization reactions require **coenzyme B_{12},** a coenzyme derived from vitamin B_{12}. The vitamin has a cyano group (or HO^- or H_2O) coordinated with cobalt. In the coenzyme, this group is replaced by a 5′-deoxyadenosyl group.

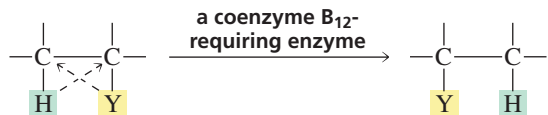
a 5′-deoxyadenosyl group

coenzyme B_{12}

Animals and plants cannot synthesize vitamin B_{12}. In fact, only a few species of bacteria can synthesize it. Humans must obtain all their vitamin B_{12} from their diet, particularly from meat. A deficiency causes pernicious anemia. Because vitamin B_{12} is needed in only very small amounts, deficiencies caused by the consumption of insufficient amounts of the vitamin are rare but have been found in vegetarians who eat no animal products. Most deficiencies are caused by the inability of the intestines to absorb the vitamin.

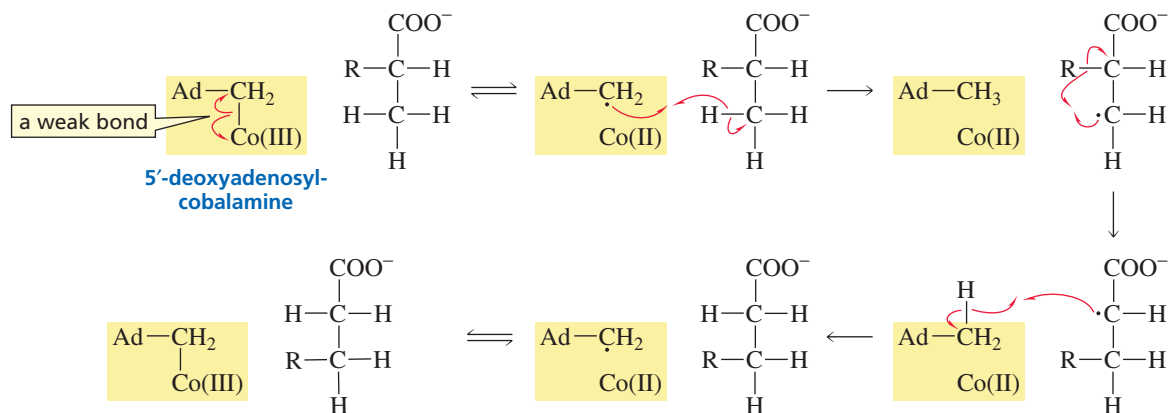
The following is an example of an enzyme-catalyzed reaction that requires coenzyme B_{12}. A mutase is an enzyme that transfers a group from one position to another.

$CH_3CH(COO^-)C(=O)SCoA$ (methylmalonyl-CoA) —[methylmalonyl-CoA mutase, coenzyme B_{12}]→ $CH_2CH_2(COO^-)C(=O)SCoA$ (succinyl-CoA)

In each of these coenzyme B_{12}-requiring reactions, a hydrogen bonded to one carbon exchanges places with a group (Y) bonded to an adjacent carbon.

Coenzyme B_{12} is required by enzymes that catalyze the exchange of a hydrogen bonded to one carbon with a group bonded to an adjacent carbon.

—C(H)—C(Y)— —[a coenzyme B_{12}-requiring enzyme]→ —C(Y)—C(H)—

For example, methylmalonyl-CoA mutase catalyzes a reaction in which the H bonded to one carbon changes places with a C(═O)SCoA group bonded to an adjacent carbon.

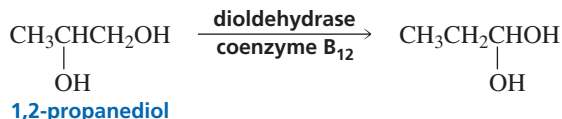
The chemistry of coenzyme B_{12} takes place at the bond joining the cobalt and the 5′-deoxyadenosyl group, which is an unusually weak bond (26 kcal/mol compared with 99 kcal/mol for a C—H bond). In the following mechanism, C(═O)SCoA is abbreviated as R.

MECHANISM FOR THE REACTION CATALYZED BY METHYLMALONYL-CoA MUTASE

- The Co—C bond breaks homolytically, forming a 5′-deoxyadenosyl radical and reducing Co(III) to Co(II).
- The 5′-deoxyadenosyl radical removes the hydrogen atom that will change place with another group.
- A group (R·) migrates from one carbon to the next, creating a new radical.
- The new radical removes a hydrogen atom from 5′-deoxyadenosine, forming the rearranged product and regenerating the 5′-deoxyadenosyl radical.
- The 5′-deoxyadenosyl radical recombines with Co(II) to regenerate the coenzyme. The enzyme–coenzyme complex is then ready for another catalytic cycle.

It is likely that all coenzyme B_{12}-requiring enzymes catalyze reactions by the same general mechanism. The role of the coenzyme is to provide a way to remove a hydrogen atom from the substrate. Once the hydrogen atom has been removed, an adjacent group can migrate to take its place. The coenzyme then gives back the hydrogen atom, delivering it to the carbon that lost the migrating group.

PROBLEM 27♦

What groups are interchanged in the following enzyme-catalyzed reaction that requires coenzyme B_{12}?

$CH_3CH(OH)CH_2OH$ (1,2-propanediol) —dioldehydrase, coenzyme B_{12}→ $CH_3CH_2CH(OH)OH$

18.13 FOLIC ACID: THE VITAMIN NEEDED FOR ONE-CARBON TRANSFER

Tetrahydrofolate (THF) is the coenzyme used by enzymes that catalyze reactions that transfer a group containing a single carbon to their substrates. The one-carbon group can be a methyl group (CH_3), a methylene group (CH_2), or a formyl group (HC=O). Tetrahydrofolate is produced by the reduction of two double bonds of folic acid (folate), its precursor vitamin. Bacteria can synthesize folate, but mammals cannot.

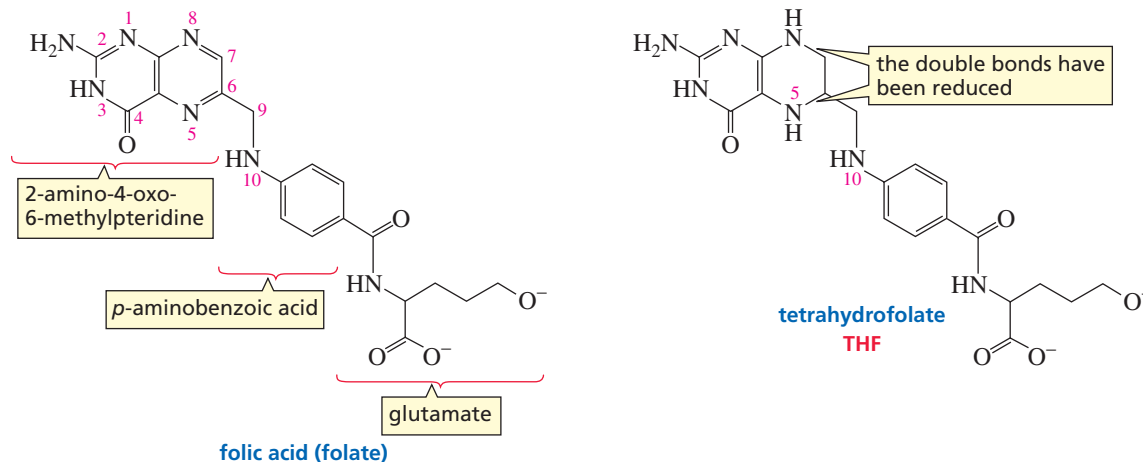
2-amino-4-oxo-6-methylpteridine

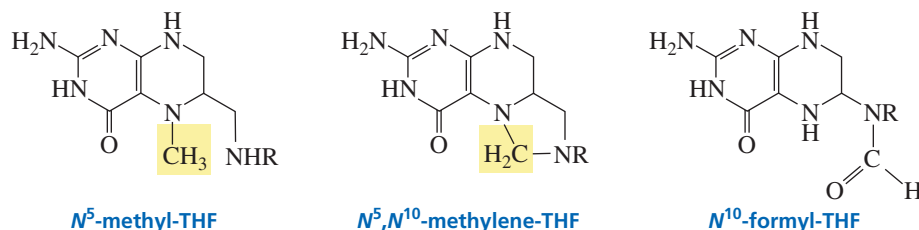
p-aminobenzoic acid

glutamate

folic acid (folate)

the double bonds have been reduced

tetrahydrofolate THF

Three THF-coenzymes are shown here. N^5-Methyl-THF transfers a methyl group, N^5,N^{10}-methylene-THF transfers a methylene group, and N^{10}-formyl-THF transfers a formyl group.

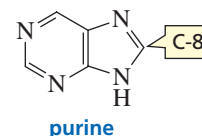
N^5-methyl-THF N^5,N^{10}-methylene-THF N^{10}-formyl-THF

A tetrahydrofolate (THF) coenzyme is required by enzymes that catalyze the transfer of a group containing one carbon to their substrates.

Glycinamide ribonucleotide (GAR) transformylase is an enzyme that requires a THF-coenzyme. The formyl group that is given to the substrate eventually ends up being the C-8 carbon of purine. Two of the four heterocyclic bases found in DNA and RNA are purines (Section 21.1).

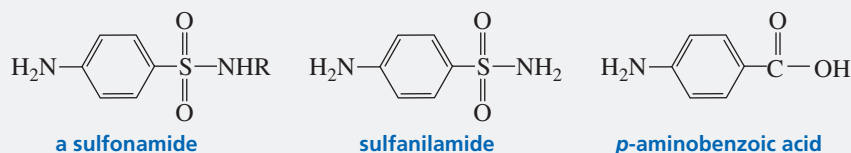
GAR + N^{10}-formyl-THF —GAR transformylase→ formyl-GAR + THF

ribose-5-phosphate ribose-5-phosphate

C-8

purine

The First Antibiotics

Sulfonamides—commonly known as sulfa drugs—were introduced clinically in 1934 as the first effective antibiotics. Donald Woods, a British bacteriologist, noticed that sulfanilamide, initially the most widely used sulfonamide, was structurally similar to *p*-aminobenzoic acid, a compound necessary for bacterial growth.

a sulfonamide — sulfanilamide — *p*-aminobenzoic acid

This suggested that sulfanilamide acts by inhibiting the enzyme that incorporates *p*-aminobenzoic acid into folic acid. Because the enzyme cannot tell the difference between sulfanilamide and *p*-aminobenzoic acid, both compounds compete for the active site of the enzyme. Without folic acid, the bacteria die. Humans are not adversely affected by the drug because they do not synthesize folate; instead, they get all their folate from their diet.

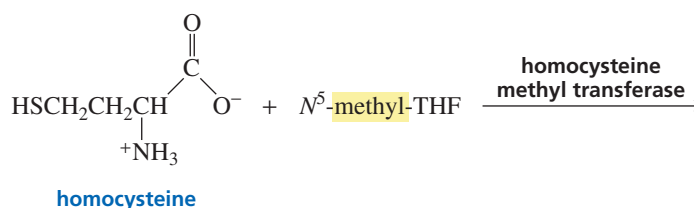
PROBLEM 28♦

Why is the coenzyme called tetrahydrofolate?

PROBLEM 29♦

What amino acid is formed by the following reaction?

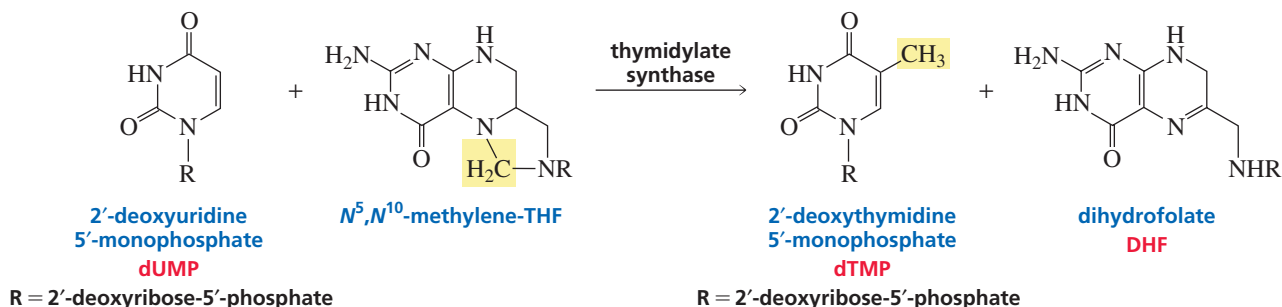
$HSCH_2CH_2CH(^+NH_3)COO^-$ + N^5-methyl-THF $\xrightarrow{\text{homocysteine methyl transferase}}$

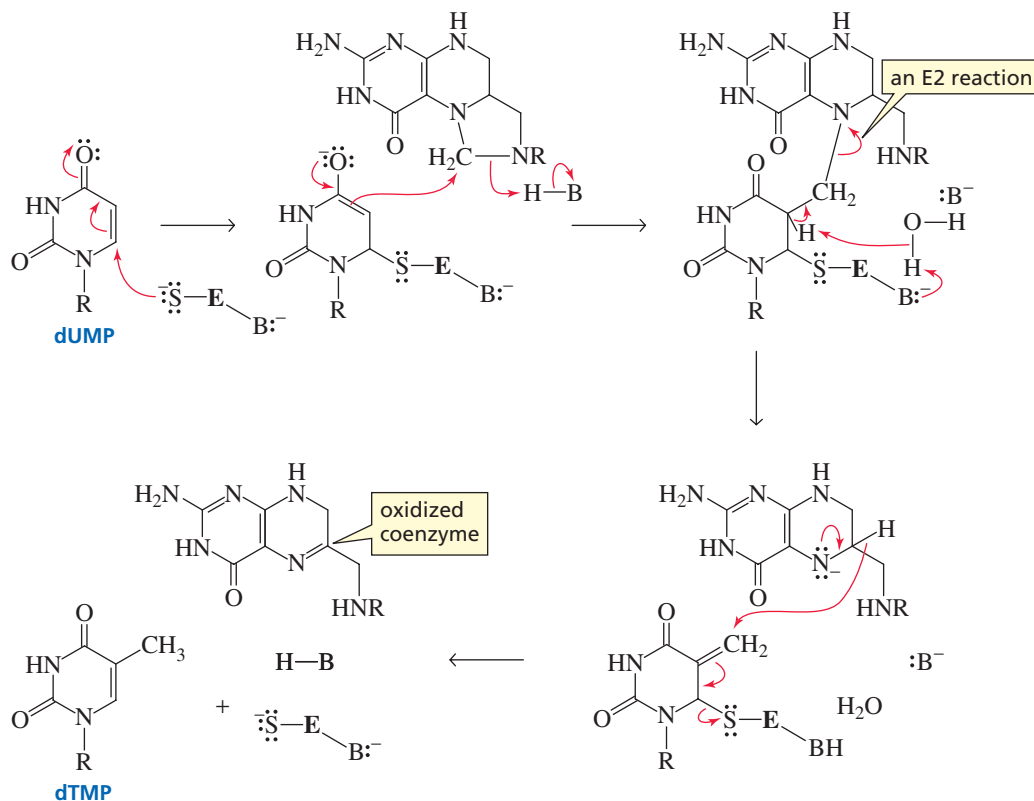
homocysteine

Thymidylate Synthase: The Enzyme That Converts U to T

The heterocyclic bases in RNA are adenine, guanine, cytosine, and uracil (A, G, C, and U). The heterocyclic bases in DNA are adenine, guanine, cytosine, and thymine (A, G, C, and T). In other words, the heterocyclic bases in RNA and DNA are the same, with one exception: RNA contains U, whereas DNA contains T. (These bases are described in Section 21.1. Why DNA contains T instead of U is explained in Section 21.10.)

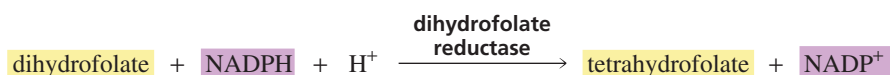
The Ts used for the biosynthesis of DNA are synthesized from Us by thymidylate synthase, an enzyme that requires the coenzyme N^5,N^{10}-methylene-THF. The actual substrate is dUMP (2′-deoxyuridine 5′-monophosphate) and the product is dTMP (2′-deoxythymidine 5′-monophosphate).

2′-deoxyuridine 5′-monophosphate **dUMP** + N^5,N^{10}-methylene-THF $\xrightarrow{\text{thymidylate synthase}}$ 2′-deoxythymidine 5′-monophosphate **dTMP** + dihydrofolate **DHF**

R = 2′-deoxyribose-5′-phosphate

Even though the only structural difference between T and U is a *methyl* group, T is synthesized by first transferring a *methylene* group to a U. The methylene group is then reduced to a methyl group. The mechanism of the reaction is shown here.

MECHANISM FOR THE REACTION CATALYZED BY THYMIDYLATE SYNTHASE

- A nucleophilic cysteine at the active site of the enzyme adds to the β-carbon of dUMP. (This is an example of conjugate addition; see Section 12.10.)
- Nucleophilic attack by the enolate ion of dUMP on the methylene group of N^5,N^{10}-methylene-THF forms a covalent bond between dUMP and the coenzyme. This is an S_N2 reaction. The leaving group has to be protonated to improve its leaving propensity.
- A base removes a proton from the α-carbon and the coenzyme is eliminated in an E2 reaction. The base is thought to be a water molecule whose basicity is increased by the O^- group of a tyrosine side chain of the enzyme (here written as $:B^-$).
- Transfer of a hydride ion from the coenzyme to the methylene group, followed by elimination of the enzyme, forms dTMP and dihydrofolate (DHF).

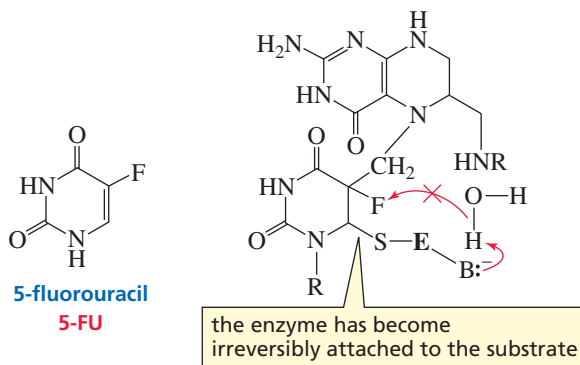
Notice that the coenzyme that transfers the methylene group to the substrate is also the reagent that subsequently reduces the methylene group to a methyl group. Because the coenzyme is the reducing agent, it is oxidized to dihydrofolate. (Recall that oxidation decreases the number of C—H bonds.) Dihydrofolate must then be reduced back to tetrahydrofolate by the enzyme dihydrofolate reductase so that tetrahydrofolate continues to be available as a coenzyme.

$$\text{dihydrofolate} + \text{NADPH} + H^+ \xrightarrow{\text{dihydrofolate reductase}} \text{tetrahydrofolate} + \text{NADP}^+$$

Cancer Chemotherapy

Cancer is the uncontrolled growth and proliferation of cells. Because cells cannot multiply if they cannot synthesize DNA, scientists have long searched for compounds that would inhibit either thymidylate synthase or dihydrofolate reductase. If a cell cannot make Ts, it cannot synthesize DNA. Inhibiting dihydrofolate reductase also prevents the synthesis of Ts because cells have a limited amount of tetrahydrofolate. If they cannot convert dihydrofolate back to tetrahydrofolate, they cannot continue to synthesize Ts.

5-Fluorouracil is a common anticancer drug that inhibits thymidylate synthase. The enzyme reacts with 5-fluorouracil in the same way it reacts with dUMP. However, the fluorine of 5-fluorouracil causes it to become permanently attached to the active site of the enzyme because fluorine is too electronegative to come off as F^+ in the elimination reaction (the third step in the mechanism on the previous page). As a consequence, the reaction stops, leaving the enzyme permanently attached to 5-fluorouracil (Figure 18.4). Because the active site of the enzyme is now blocked with 5-fluorouracil, it cannot bind dUMP. Therefore, dTMP can no longer be synthesized and, without dTMP, DNA cannot be synthesized. Consequently, cancer cells undergo "thymineless" death.

5-fluorouracil
5-FU

the enzyme has become irreversibly attached to the substrate

Unfortunately, most anticancer drugs cannot discriminate between diseased and normal cells, so most cancer chemotherapy is accompanied by debilitating side effects. However, because cancer cells divide more rapidly than normal cells, they are harder hit by cancer-fighting chemotherapeutic agents than normal cells are.

5-Fluorouracil is a **mechanism-based inhibitor:** it inactivates the enzyme by taking part in the normal catalytic mechanism. It is also called a **suicide inhibitor** because the enzyme effectively "commits suicide" by reacting with the inhibitor. The therapeutic use of 5-fluorouracil illustrates the importance of knowing the mechanism for enzyme-catalyzed reactions. If scientists know the mechanism of a reaction, they may be able to design an inhibitor to turn the reaction off at a certain step.

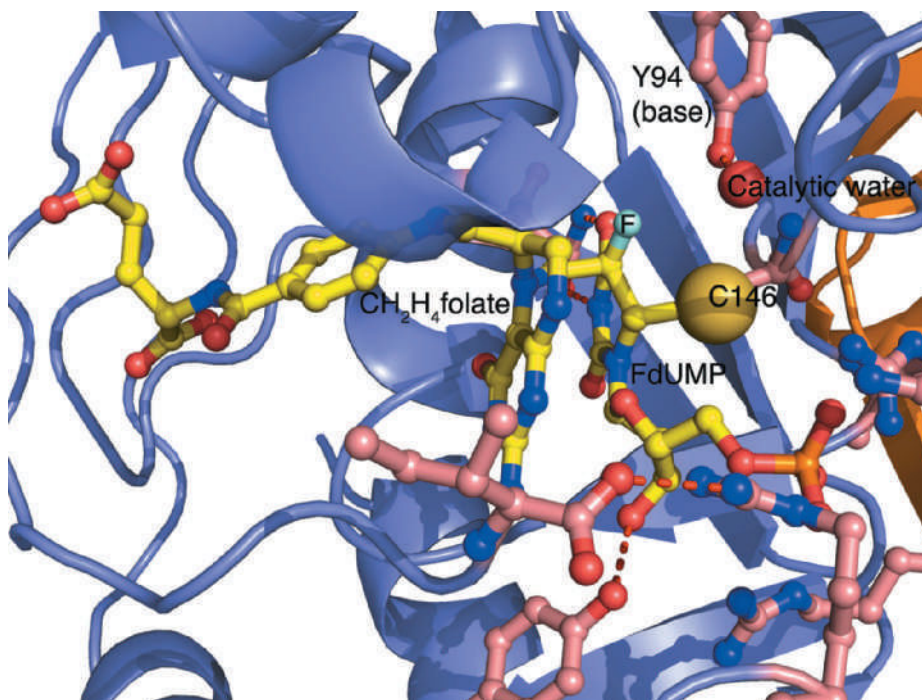
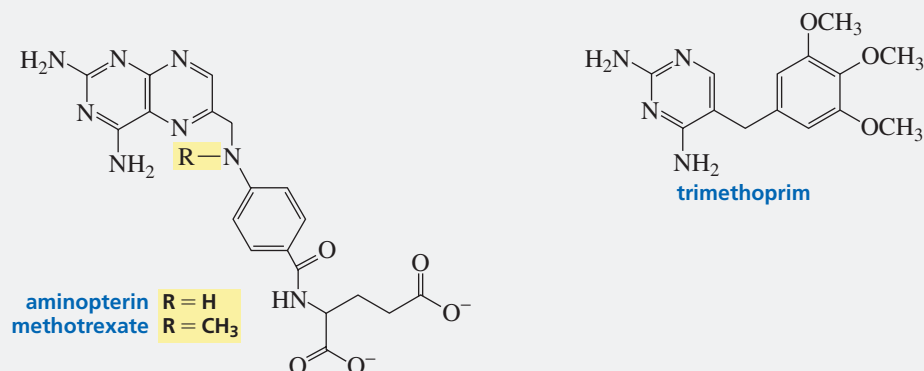



Figure 18.4
The tetrahydrofolate coenzyme and 5-fluoro-dUMP that is covalently bonded to cysteine 146 of the enzyme are shown in yellow. The fluorine (turquoise), tyrosine 94, and the catalytic water molecule are also visible. The side chains that hold the coenzyme in the proper position at the active site are pink.

Competitive Inhibitors

Aminopterin and methotrexate are anticancer drugs that are inhibitors of dihydrofolate reductase. Because their structures are similar to that of dihydrofolate, they compete with it for binding to the active site of the enzyme. Because they bind 1000 times more tightly to the enzyme than dihydrofolate does, they win the competition and, therefore, inhibit the enzyme's activity. These two compounds are examples of **competitive inhibitors.**

aminopterin R = H
methotrexate R = CH_3

trimethoprim

Because aminopterin and methotrexate inhibit the synthesis of THF, they interfere with the synthesis of any compound that requires a THF-coenzyme in one of the steps of its synthesis. Thus, not only do they prevent the synthesis of thymidine, they also inhibit the synthesis of adenine and guanine—the purines needed for the synthesis of DNA—because their synthesis also requires a THF-coenzyme (see page 37). One clinical technique used to fight cancer calls for the patient to be given a lethal dose of methotrexate. Then, after the cancer cells have died, the patient is "saved" by being given N^5-formyl-THF.

Trimethoprim is used as an antibiotic because it binds to bacterial dihydrofolate reductase much more tightly than to mammalian dihydrofolate reductase.

Cancer Drugs and Side Effects

Scientists are searching for drugs that can discriminate between diseased and normal cells so that cancer chemotherapy will not be accompanied by debilitating side effects. A new drug, now in clinical trials, is able to deliver a very toxic agent only to cancer cells.

Herceptin has been used since 1998 to treat certain kinds of breast cancers. Recently, scientists have been able to attach it to another anticancer drug that is so toxic it cannot be used directly. Once Herceptin has bound to a breast cancer cell, it releases the poisonous agent to kill the cell. The survival time for women with advanced breast cancer enrolled in the clinical trials for this combined drug has been found to be almost a year longer, with much fewer side effects, than for women treated with Herceptin and other cancer drugs.

PROBLEM 30♦

How do the structures of tetrahydrofolate and aminopterin differ?

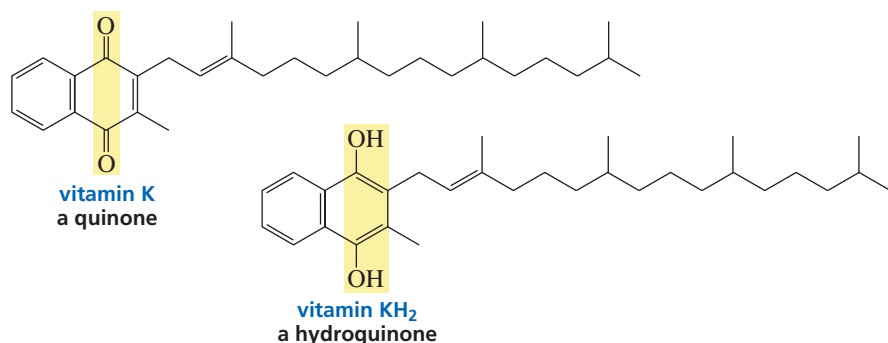
PROBLEM 31

What is the source of the methyl group in thymidine?

18.14 VITAMIN K: THE VITAMIN NEEDED FOR CARBOXYLATION OF GLUTAMATE

Vitamin K is required for proper blood clotting. The letter K comes from *koagulation*, which is German for "clotting." Vitamin K is found in the leaves of green plants. Deficiencies are rare because the vitamin is also synthesized by intestinal bacteria. **Vitamin KH$_2$** (the hydroquinone of vitamin K) is the coenzyme form of the vitamin.

vitamin K
a quinone

vitamin KH_2
a hydroquinone

A series of reactions involving six proteins causes blood to clot. The process requires these proteins to bind Ca^{2+}. γ-Carboxyglutamates bind Ca^{2+} much more effectively than glutamates do, so glutamates need to be converted to γ-glutamates in order for blood to clot.

Vitamin KH_2 is required by the enzyme that catalyzes the carboxylation of the γ-carbon of a glutamate side chain.

Vitamin KH_2 is the coenzyme for the enzyme that converts a glutamate to a γ-carboxyglutamate. The coenzyme provides a strong base that can remove a proton from the γ-carbon so that it can react with CO_2. The enzyme uses CO_2 for the carboxyl group that it puts on the glutamate side chain. All the proteins responsible for blood clotting have several glutamates near their N-terminal ends. For example, prothrombin, a blood-clotting protein, has glutamates at positions 7, 8, 15, 17, 20, 21, 26, 27, 30, and 33.

γ-carbon

enzyme
vitamin KH_2

Ca^{2+}

glutamate side chain

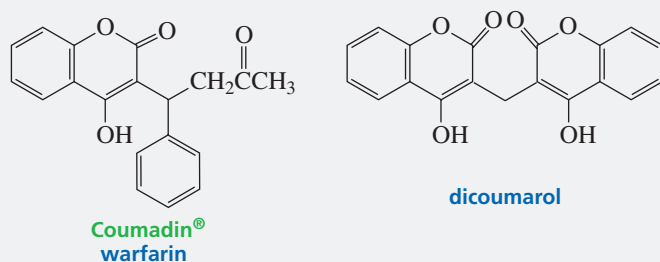
γ-carboxyglutamate side chain

calcium complex

Anticoagulants

Warfarin and dicoumarol are used clinically as anticoagulants. In the process of forming the base needed to remove a proton from the γ-carbon of glutamate, vitamin KH_2 is converted to vitamin K epoxide. Warfarin and dicoumerol prevent blood clotting because they inhibit the enzyme that converts vitamin K epoxide back to vitamin KH_2 by binding to the enzyme's active site. Because the enzyme cannot tell the difference between these two compounds and vitamin K epoxide, the compounds are *competitive inhibitors*. Warfarin is also commonly used as a rat poison, causing death by internal bleeding.

Coumadin®
warfarin

dicoumarol

Vitamin E, too, has recently been found to be an anticoagulant. It inhibits the enzyme that carboxylates glutamate residues.

Too Much Broccoli

Two women with diseases characterized by abnormal blood clotting reported that they did not improve when they were given Coumadin. When questioned about their diets, one woman said that she ate at least a pound of broccoli every day, and the other ate broccoli soup and a broccoli salad every day. When broccoli was removed from their diets, Coumadin was effective in preventing the abnormal clotting of their blood. Because broccoli is high in vitamin K, these patients had been getting enough dietary vitamin K to compete successfully with the drug for the enzyme's active site, thereby making the drug ineffective.

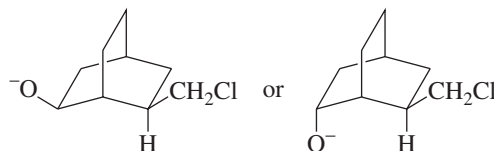
SOME IMPORTANT THINGS TO REMEMBER

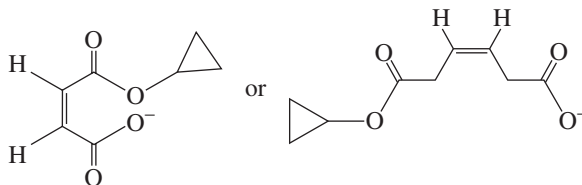
- A **catalyst** increases the rate of a chemical reaction but is not consumed or changed in the reaction.
- An **acid catalyst** increases the rate of a reaction by donating a proton to a reactant.
- A **base catalyst** increases the rate of a reaction by removing a proton from a reactant.
- A **nucleophilic catalyst** increases the rate of a reaction by acting as a nucleophile: it forms an intermediate by forming a covalent bond with a reactant.
- Stabilization of a charge by an opposite charge is called **electrostatic catalysis.**
- The rate of a chemical reaction is determined by the number of collisions between two molecules or between two groups in the same molecule, with sufficient energy and with the proper orientation in a given period of time.
- Most biological catalysts are **enzymes.** The reactant of an enzyme-catalyzed reaction is called a **substrate.** The enzyme specifically binds the substrate at its **active site**; all the bond-making and bond-breaking steps of the reaction occur while it is at the active site.
- The specificity of an enzyme for its substrate is an example of **molecular recognition.**
- **Induced fit** is the change in conformation of the enzyme that occurs when it binds the substrate.
- Two important factors contribute to the remarkable catalytic ability of enzymes: 1. The reacting groups are brought together at the active site in the proper orientation for reaction. 2. The amino acid side chains are well positioned relative to the substrate, where they are needed for catalysis and transition state stabilization.
- **Coenzymes** play a variety of chemical roles that the amino acid side chains of enzymes cannot perform. Some function as oxidizing and reducing agents; some allow electrons to be delocalized; some activate groups for further reaction; and some provide good nucleophiles or strong bases needed for a reaction.
- Coenzymes are derived from **vitamins,** which are substances needed in small amounts for normal body function that the body cannot synthesize.
- All the water-soluble vitamins except vitamin C are precursors of coenzymes. Vitamin K is the only water-insoluble vitamin that is a precursor of a coenzyme.
- **Catabolic reactions** break down complex biomolecules to provide energy and simple molecules, whereas **anabolic reactions** require energy and lead to the synthesis of complex biomolecules.
- **NAD^+** and **FAD** are coenzymes used to catalyze oxidation reactions.
- **NADPH** and **$FADH_2$** are coenzymes used to catalyze reduction reactions.
- All the chemistry of the **pyridine nucleotide coenzymes** takes place at the 4-position of the pyridine ring. All the chemistry of the **flavin coenzymes** takes place on the flavin ring.
- **Thiamine pyrophosphate (TPP)** is the coenzyme required by enzymes that catalyze the transfer of an acyl group.
- **Biotin** is the coenzyme required by enzymes that catalyze the carboxylation of a carbon adjacent to a carbonyl group.
- **Pyridoxal phosphate (PLP)** is the coenzyme required by enzymes that catalyze certain reactions of amino acids, such as decarboxylation, transamination, and racemization.
- In a **transimination reaction,** one imine is converted into another imine; in a **transamination reaction,** the amino group is removed from a substrate and transferred to another molecule, leaving a keto group in its place.
- In a **coenzyme B_{12}**-requiring enzymatic reaction, a group bonded to one carbon changes places with a hydrogen bonded to an adjacent carbon.

- **Tetrahydrofolate (THF)** is the coenzyme used by enzymes catalyzing reactions that transfer a group containing a single carbon—methyl, methylene, or formyl—to their substrates.
- **Vitamin KH_2** is the coenzyme for the enzyme that catalyzes the carboxylation of the γ-carbon of glutamate side chains, a reaction required for blood clotting.
- A **suicide inhibitor** inactivates an enzyme by taking part in the catalytic mechanism.
- A **competitive inhibitor** competes with the substrate for binding at the active site of the enzyme.

PROBLEMS

32. Which of the following compounds would eliminate HCl more rapidly in a basic solution?

^{-}O ... CH_2Cl, H or ... CH_2Cl, O^{-}, H

33. Which compound would form an anhydride more rapidly?

H, O, O, O^{-}, H, O or H H, O, O, O, O^{-}

34. From what vitamins are the following coenzymes derived?

a. Thiamine pyrophosphate **b.** Coenzyme A **c.** $FADH_2$ **d.** NADPH

35. Answer the following:

a. What coenzyme transfers an acyl group from one substrate to another?
b. What is the function of FAD in the pyruvate dehydrogenase complex?
c. What is the function of NAD^+ in the pyruvate dehydrogenase complex?
d. What reaction necessary for proper blood clotting is catalyzed by vitamin KH_2?
e. What coenzymes are used for carboxylation reactions?
f. What kinds of substrates do the carboxylating coenzymes work on?

36. For each of the following reactions, name both the enzyme that catalyzes the reaction and the required coenzyme:

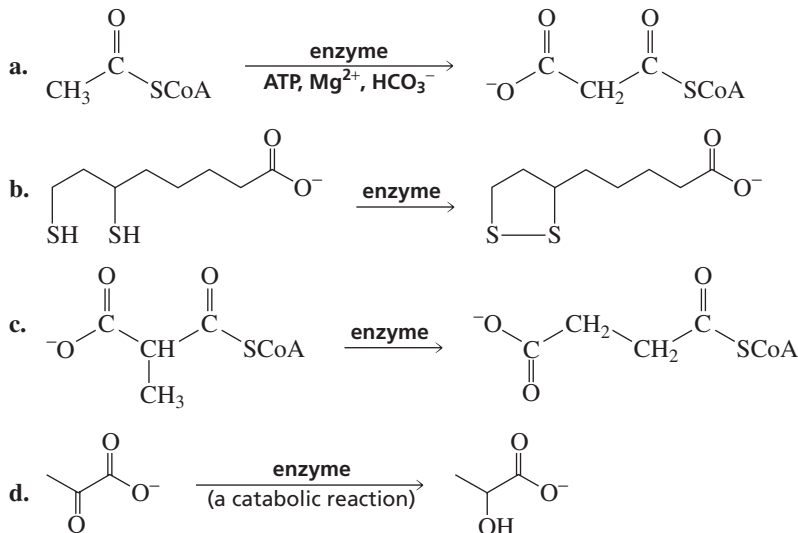
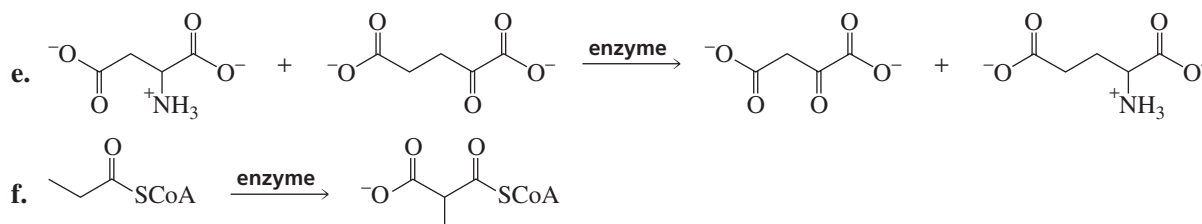
a. $CH_3C(=O)SCoA$ —enzyme; ATP, Mg^{2+}, HCO_3^-→ $^{-}OC(=O)CH_2C(=O)SCoA$

b. SH SH, O, O^{-} —enzyme→ S—S, O, O^{-}

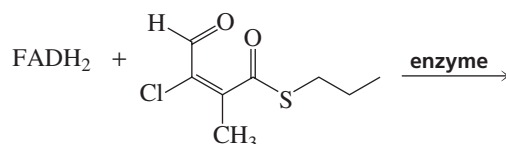
c. $^{-}OC(=O)CH(CH_3)C(=O)SCoA$ —enzyme→ $^{-}OC(=O)CH_2CH_2C(=O)SCoA$

d. O, O^{-}, O —enzyme (a catabolic reaction)→ O, O^{-}, OH

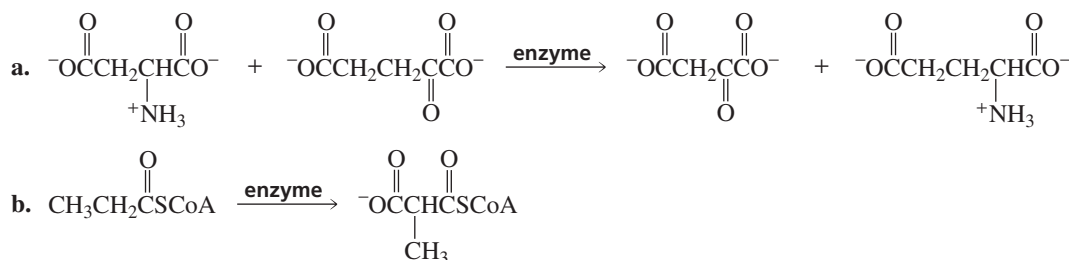
e. $^{-}O_2CCH_2CH(\overset{+}{N}H_3)CO_2^{-}$ + $^{-}O_2CCH_2CH_2COCO_2^{-}$ $\xrightarrow{\text{enzyme}}$ $^{-}O_2CCH_2COCO_2^{-}$ + $^{-}O_2CCH_2CH_2CH(\overset{+}{N}H_3)CO_2^{-}$

f. $CH_3CH_2C(=O)SCoA$ $\xrightarrow{\text{enzyme}}$ $^{-}OC(=O)CH(CH_3)C(=O)SCoA$

37. Explain why serine proteases do not catalyze hydrolysis if the amino acid at the hydrolysis site is a D-amino acid. Trypsin, for example, cleaves on the C-side of L-Arg and L-Lys, but not on the C-side of D-Arg and D-Lys.

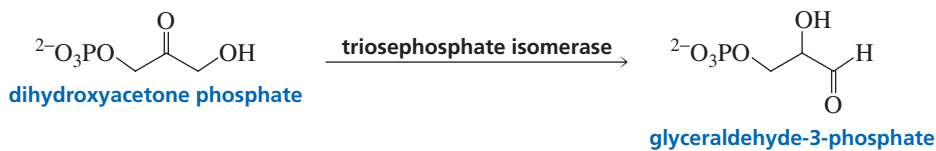
38. What is the product of the following reaction?

$FADH_2$ + H(O=)C–C(Cl)=C(CH_3)–C(=O)–S–$CH_2CH_2CH_3$ $\xrightarrow{\text{enzyme}}$

39. For each of the following enzyme-catalyzed reactions, name the required coenzyme:

a. $^{-}OCCH_2CHCO^{-}$ (with O, O; $^{+}NH_3$) + $^{-}OCCH_2CH_2CCO^{-}$ (with O, O; O) $\xrightarrow{\text{enzyme}}$ $^{-}OCCH_2CCO^{-}$ (with O, O; O) + $^{-}OCCH_2CH_2CHCO^{-}$ (with O, O; $^{+}NH_3$)

b. $CH_3CH_2\overset{O}{\overset{\|}{C}}SCoA$ $\xrightarrow{\text{enzyme}}$ $^{-}O\overset{O}{\overset{\|}{C}}CH\overset{O}{\overset{\|}{C}}SCoA$ (CH with CH_3)

40. Triosephosphate isomerase (TIM) catalyzes the conversion of dihydroxyacetone phosphate to glyceraldehyde-3-phosphate. The enzyme's catalytic groups are Glu 165 and His 95. In the first step of the reaction, these catalytic groups function as a base and an acid catalyst, respectively. Propose a mechanism for the reaction.

$^{2-}O_3POCH_2C(=O)CH_2OH$ $\xrightarrow{\text{triosephosphate isomerase}}$ $^{2-}O_3POCH_2CH(OH)C(=O)H$

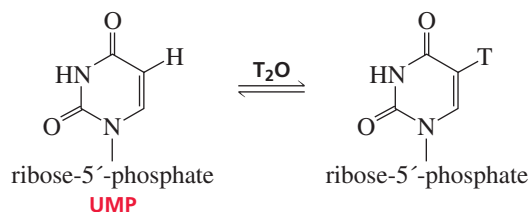
dihydroxyacetone phosphate — glyceraldehyde-3-phosphate

41. In glycolysis, why must glucose-6-phosphate isomerize to fructose-6-phosphate before the cleavage reaction with aldolase occurs?

42. What acyl groups have we seen transferred by reactions that require thiamine pyrophosphate as a coenzyme? (*Hint:* See Problems 16, 17, 18, 20, 44, and 45.)

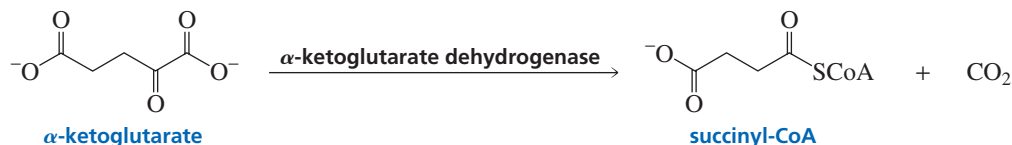
43. When UMP is dissolved in T_2O, exchange of T for H occurs at the 5-position. Propose a mechanism for this exchange. (T is ^{3}H, a hydrogen with two neutrons.)

UMP (uracil, H at 5-position; N1–ribose-5′-phosphate) $\underset{}{\overset{T_2O}{\rightleftharpoons}}$ (uracil, T at 5-position; N1–ribose-5′-phosphate)

ribose-5′-phosphate — ribose-5′-phosphate

UMP

44. Five coenzymes are required by α-ketoglutarate dehydrogenase, the enzyme in the citric acid cycle that converts α-ketoglutarate to succinyl-CoA.

a. Identify the coenzymes. **b.** Propose a mechanism for the reaction.

α-ketoglutarate —(α-ketoglutarate dehydrogenase)→ succinyl-CoA + CO_2

45. When transaminated, the three branched-chain amino acids (valine, leucine, and isoleucine) form compounds that have the characteristic odor of maple syrup. An enzyme known as branched-chain α-keto acid dehydrogenase converts these compounds into CoA esters. People who do not have this enzyme have the genetic disease known as maple syrup urine disease, so called because their urine smells like maple syrup.

a. Draw the compounds that smell like maple syrup.

b. Draw the CoA esters.

c. Branched-chain α-keto acid dehydrogenase has five coenzymes. Identify them.

d. Suggest a way to treat maple syrup urine disease.

46. Aldolase shows no activity if it is incubated with iodoacetic acid before fructose-1,6-bisphosphate is added to the reaction mixture. What could cause this loss of activity?

19 The Organic Chemistry of the Metabolic Pathways

You are what you eat.

The reactions that living organisms carry out to obtain the energy they need and to synthesize the compounds they require are collectively known as **metabolism.** *Metabolism can be divided into two parts: catabolism and anabolism. Catabolic reactions convert complex nutrient molecules into simple molecules that can be used for synthesis. Anabolic reactions synthesize complex biomolecules from simpler precursor molecules. Catabolism comes from the Greek word* katabol, *which means "throwing down."*

A catabolic pathway is a series of sequential reactions that converts a complex molecule into simple molecules. Catabolic pathways produce energy. An anabolic pathway is a series of sequential reactions that converts simple molecules into a complex molecule. Anabolic pathways require energy.

catabolism: *complex molecule* $\longrightarrow$ *simple molecules + energy*
anabolism: *simple molecules + energy* $\longrightarrow$ *complex molecule*

It is important to remember that almost every reaction that occurs in a living system is catalyzed by an enzyme. The enzyme holds the reactants and any necessary coenzymes in place, orienting the reacting functional groups and the amino acid side chain catalysts in a way that allows the enzyme-catalyzed reaction to take place (Section 18.2).

Most of the reactions described in this chapter will be familiar to you. If you take the time to refer back to the sections cited and review these reactions, you will see that many of the organic reactions done by cells are the same as the organic reactions done by chemists.

Differences in Metabolism

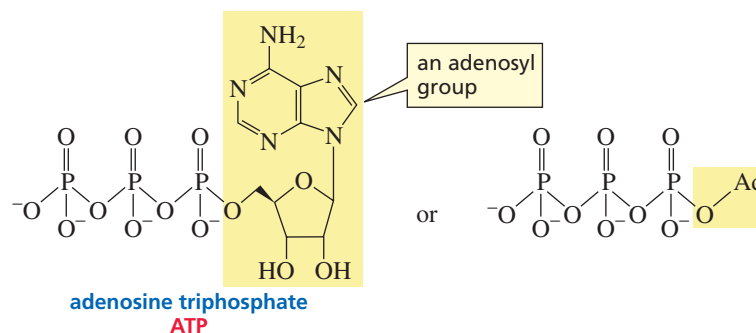
Humans do not necessarily metabolize compounds in the same way as other species do. This becomes a significant problem when drugs are tested on animals. For example, chocolate is metabolized to different compounds in humans and in dogs. The metabolites produced in humans are nontoxic, whereas those produced in dogs can be highly toxic. Differences in metabolism have been found even within the same species. For example, isoniazid—an antituberculosis drug—is metabolized by Eskimos much faster than by Egyptians. Current research is showing that men and women metabolize certain drugs differently. For example, kappa opioids—a class of painkillers—have been found to be about twice as effective in women as they are in men.

19.1 ATP IS USED FOR PHOSPHORYL TRANSFER REACTIONS

All cells require energy to live and reproduce. They get the energy they need from nutrients that they convert into a chemically useful form. The most important repository of chemical energy is **adenosine 5′-triphosphate (ATP).** The importance of ATP to biological reactions is reflected in its turnover rate in humans: each day, a person uses an amount of ATP equivalent to his or her body weight. (“Ad” represents the adenosyl group.)

an adenosyl group

or

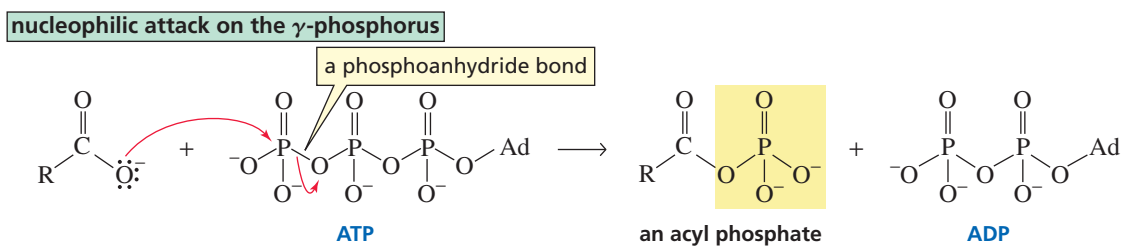
adenosine triphosphate
ATP

We have seen that phosphoryl transfer reactions can be used to activate a compound for a reaction by putting a good leaving group on it (Sections 9.3 and 11.16).

Phosporyl transfer reactions can occur in one of three ways. Each one involves an S_N2 reaction that breaks a phosphoanhydride bond (because the phosphoanhydride bond is weaker than the π bond).

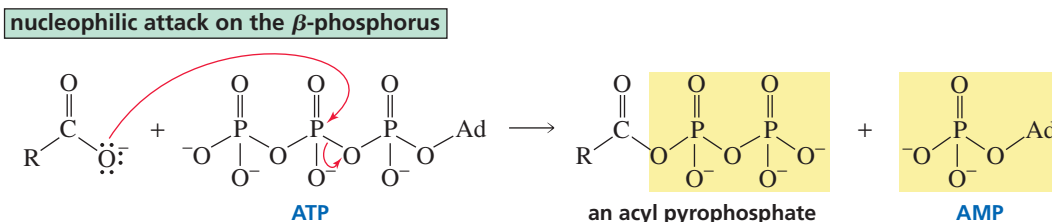
A nucleophile, such as an alcohol or a carboxylate ion, can attack the γ-phosphorus (the terminal phosphorus) of ATP, forming an **acyl phosphate.**

nucleophilic attack on the γ-phosphorus

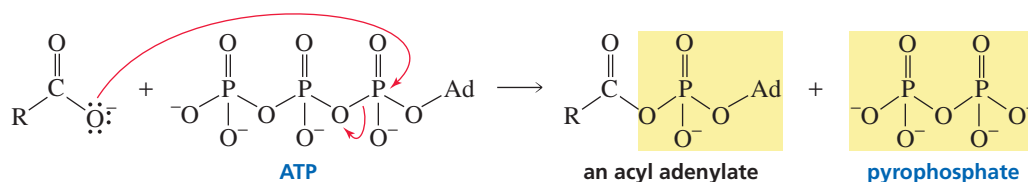
a phosphoanhydride bond

ATP — an acyl phosphate — ADP

A nucleophile can attack the β-phosphorus of ATP, forming an **acyl pyrophosphate.**

nucleophilic attack on the β-phosphorus

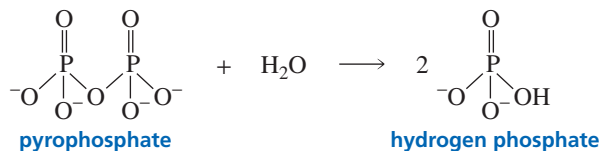
ATP — an acyl pyrophosphate — AMP

A nucleophile can attack the α-phosphorus of ATP, forming an **acyl adenylate.**

nucleophilic attack on the α-phosphorus

ATP — an acyl adenylate — pyrophosphate

Each of the preceding reactions is an S_N2 reaction that puts a good leaving group on the attacking nucleophile.

ATP provides a reaction pathway involving a good leaving group for a reaction that cannot occur (or would occur very slowly) because of a poor leaving group.

Which phosphorus the nucleophile attacks depends on the enzyme catalyzing the reaction. Notice that when a nucleophile attacks the γ-phosphorus, the side product is adenosine diphosphate (ADP), but when it attacks the α-phosphorus, the side product is pyrophosphate. When pyrophosphate is formed, it is subsequently hydrolyzed to two equivalents of hydrogen phosphate. We have seen that removing a reaction product from the reaction mixture drives the reaction that forms the product to the right (Section 5.5).

pyrophosphate + H_2O $\longrightarrow$ 2 hydrogen phosphate

Therefore, if it is essential that an enzyme-catalyzed reaction is driven to completion, the nucleophile will attack the α-phosphorus of ATP. For example, both the reaction that links nucleotide subunits to form DNA and RNA and the reaction that binds an amino acid to a tRNA (the first step in translating RNA into a protein) involve nucleophilic attack on the α-phosphorus (Sections 21.2 and 21.8). If these reactions were not driven to completion, the genetic information in DNA would not be preserved, and proteins would be synthesized that would not have the correct sequence of amino acids.

Why Did Nature Choose Phosphates?

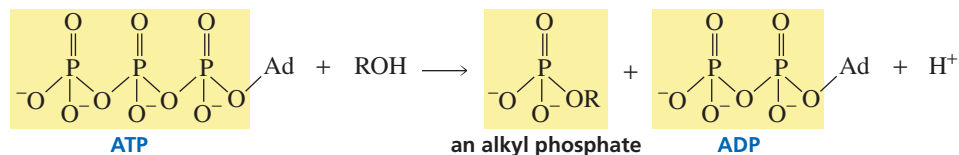
Anhydrides of phosphoric acid and esters of phosphoric acid dominate the organic chemistry of the biological world, but phosphates are rarely used in organic chemistry in the laboratory. Instead, we have seen that one of the preferred leaving groups in nonbiological reactions is a halide ion (Section 8.1).

Why did nature choose phosphates? There are several reasons. To keep a molecule from leaking through a membrane, it should be charged; to prevent reactive nucleophiles from approaching a molecule, it should be negatively charged; and to link the bases in RNA and DNA, the linking molecule needs two functional groups (Section 21.1). Phosphoric acid, with its three OH groups, fits all these requirements; it can use two of its OH groups to link the bases, and the third OH group is negatively charged at physiological pH. In addition, the reactions of nucleophiles with phosphoanhydrides can be irreversible, which is an important attribute of many biological reactions.

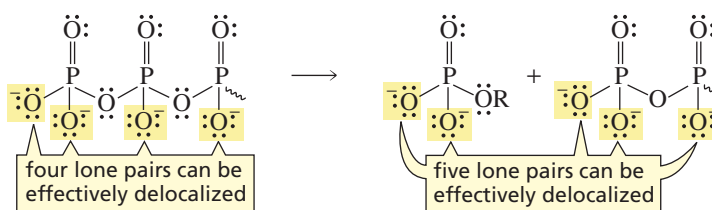
19.2 THE "HIGH-ENERGY" CHARACTER OF PHOSPHOANHYDRIDE BONDS

The reaction of a nucleophile (such as ROH) with ATP is a highly exergonic reaction. Therefore, phosphoanhydride bonds are called **high-energy bonds.** The term *high-energy* in this context means that a lot of energy is released when a phosphoanhydride bond is broken.

Why is the reaction of a nucleophile with ATP so exergonic? In other words, why is the $\Delta G^{\circ\prime}$ value large and negative?* A large, negative $\Delta G^{\circ\prime}$ means that the products of the reaction are much more stable than the reactants. Let's look at the reactants and products of the following reaction to see why this is so.

ATP + ROH ⟶ an alkyl phosphate + ADP + H^+

Three factors contribute to the greater stability of the products (ADP and the alkyl phosphate) compared to the reactants (ATP and the alcohol):

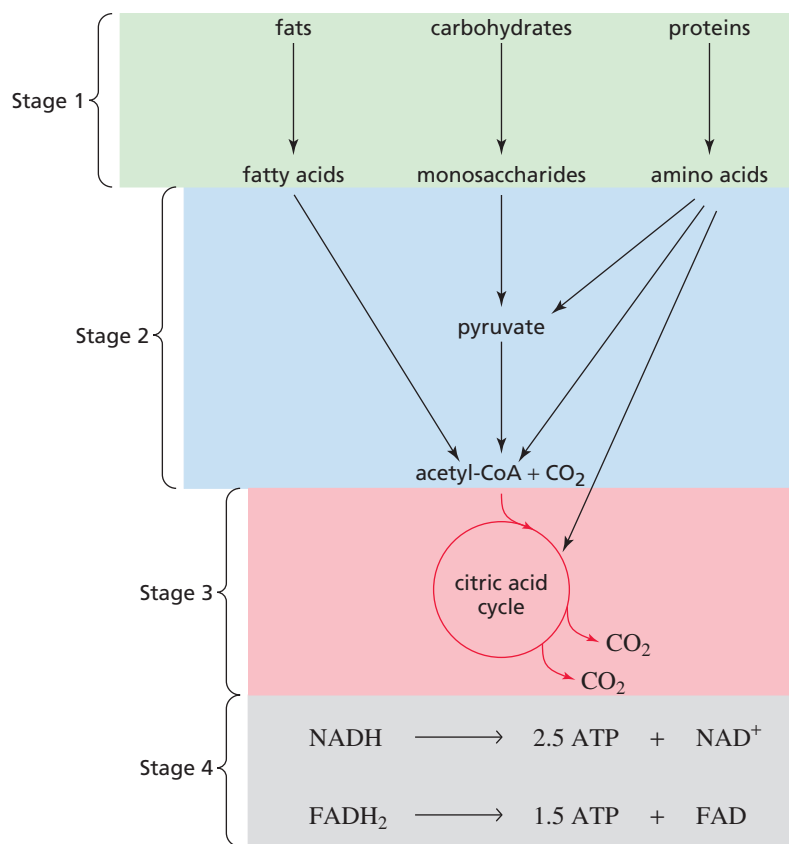
1. **Greater electrostatic repulsion in ATP.** At physiological pH (7.4), ATP has 3.3 negative charges, ADP has 2.8 negative charges, and the alkyl phosphate has 1.8 negative charges. (One of the OH groups in each molecule is not fully dissociated.) Because of ATP's greater negative charge, the electrostatic repulsion is greater in ATP than in either of the products. Electrostatic repulsions destabilize a molecule.
2. **Greater solvation stabilization in the products.** Negatively charged ions are stabilized in an aqueous solution by solvation (Section 3.8). Because the reactant has 3.3 negative charges, whereas the sum of the negative charges on the products is 4.6 (2.8 + 1.8), there is greater solvation stabilization in the products than in the reactant.
3. **Greater electron delocalization in the products.** A lone pair on the oxygen joining two phosphorus atoms is not effectively delocalized because delocalization would put a partial positive charge on an oxygen. When the phosphoanhydride bond breaks, one additional lone pair can be effectively delocalized. Electron delocalization stabilizes a molecule (Section 7.6).

four lone pairs can be effectively delocalized ⟶ five lone pairs can be effectively delocalized

19.3 THE FOUR STAGES OF CATABOLISM

The reactants required for all life processes ultimately come from our diet. In that sense, we really are what we eat. Mammalian nutrition requires fats, carbohydrates, and proteins in addition to the vitamins discussed in Chapter 18.

Catabolism can be divided into four stages (Figure 19.1). The *first stage of catabolism* is called digestion. In this stage, the fats, carbohydrates, and proteins we consume are hydrolyzed to fatty acids, monosaccharides, and amino acids, respectively. These reactions occur in the mouth, stomach, and small intestine.

In the *second stage of catabolism*, the products obtained from the first stage—fatty acids, monosaccharides, and amino acids—are converted to compounds that can enter the citric acid cycle. The only such compounds are (1) *citric acid cycle intermediates* (that is, compounds that take part in the cycle itself), (2) *acetyl-CoA,* and (3) *pyruvate* (because it can be converted to acetyl-CoA).

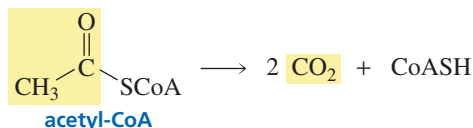
*The prime in $\Delta G^{\circ\prime}$ indicates that two additional parameters have been added to the definition of ΔG° in Section 5.4: the reaction occurs in aqueous solution at pH = 7, and the concentration of water is assumed to be constant.

In the first stage of catabolism, fats, carbohydrates, and proteins are hydrolyzed to fatty acids, monosaccharides, and amino acids.

In the second stage of catabolism, the products obtained from the first stage are converted to compounds that can enter the citric acid cycle.

◀ Figure 19.1
The four stages of catabolism: 1. digestion; 2. conversion of the products of the first stage to compounds that can enter the citric acid cycle; 3. the citric acid cycle; and 4. oxidative phosphorylation.

The *third stage of catabolism* is the citric acid cycle. In this cycle, the acetyl group of each molecule of acetyl-CoA is converted to two molecules of CO_2.

$$CH_3C(=O)SCoA \longrightarrow 2\ CO_2 + CoASH$$

acetyl-CoA

The citric acid cycle is the third stage of catabolism.

We have seen that cells get the energy they need by using nutrient molecules to make ATP. Only a small amount of ATP is formed in the first three stages of catabolism—most ATP is formed in the fourth stage. (You will be able to see this when you finish the chapter and can compare the answers to Problems 34–37.)

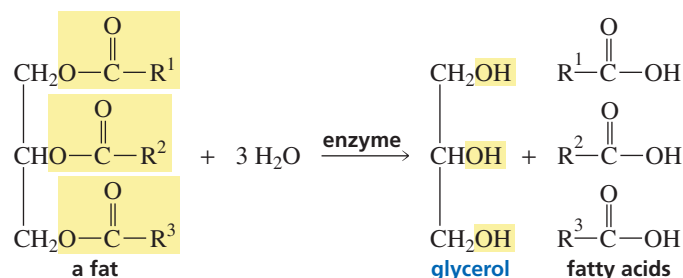
We will see that many catabolic reactions are oxidation reactions. In the *fourth stage of catabolism*, every molecule of NADH formed in one of the earlier stages of catabolism (formed when NAD^+ is used to carry out an oxidation reaction) is converted to 2.5 molecules of ATP in a process called *oxidative phosphorylation*. Oxidative phosphorylation also converts every molecule of $FADH_2$ formed in the earlier stages of catabolism (when FAD is used to carry out an oxidation reaction) to 1.5 molecules of ATP. Thus, most of the energy (ATP) that is provided by fats, carbohydrates, and proteins is obtained in the fourth stage of catabolism.

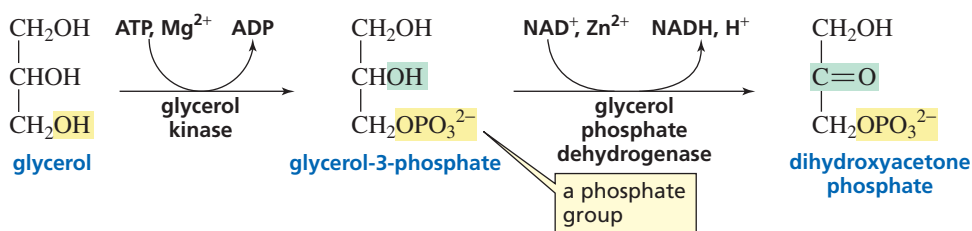
Oxidative phosphorylation is the fourth stage of catabolism.

Cells convert nutrients to ATP.

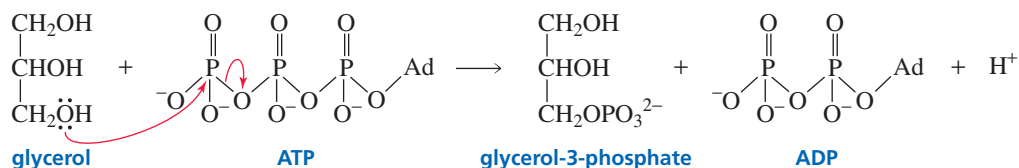
19.4 THE CATABOLISM OF FATS

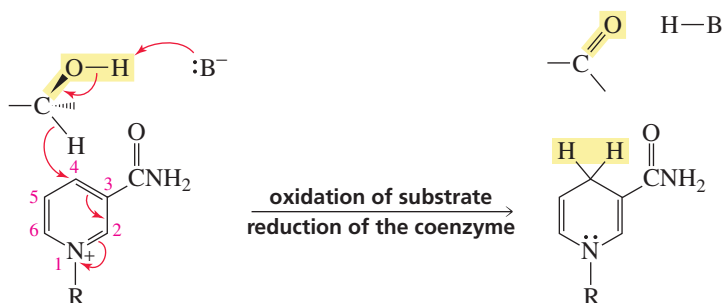
In the first stage of fat catabolism, the fat's three ester groups are hydrolyzed by an enzyme-catalyzed reaction to glycerol and three fatty acid molecules (Section 11.7).

a fat + $3\,H_2O$ —enzyme→ glycerol + fatty acids (R^1COOH, R^2COOH, R^3COOH)

The following reaction sequence shows what happens to glycerol, one of the products of the preceding reaction, in the second stage of catabolism. Notice that when biochemical reactions are written, the only structures typically shown are those of the primary reactant and primary product. The names of other reactants and products are abbreviated and placed on a curved arrow that intersects the reaction arrow.

glycerol —(ATP, Mg^{2+} → ADP; glycerol kinase)→ glycerol-3-phosphate —(NAD^+, Zn^{2+} → NADH, H^+; glycerol phosphate dehydrogenase)→ dihydroxyacetone phosphate

a phosphate group

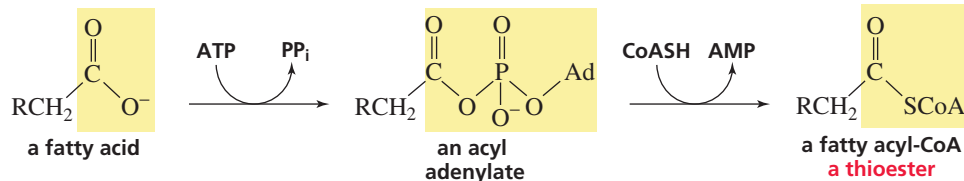
- In the first step, an OH group of glycerol reacts with ATP to form glycerol-3-phosphate; the mechanism is shown below. The enzyme that catalyzes this reaction is called glycerol kinase. A *kinase* is an enzyme that puts a phosphate group on its substrate; thus, glycerol kinase puts a phosphate group on glycerol. Notice that this ATP-requiring enzyme also requires Mg^{2+} (Section 11.16).

glycerol + ATP ⟶ glycerol-3-phosphate + ADP + H^+

- In the second step, the secondary alcohol group of glycerol-3-phosphate is oxidized by NAD^+ to a ketone. The enzyme that catalyzes this reaction is called glycerol phosphate dehydrogenase. A *dehydrogenase* is an enzyme that oxidizes its substrate (Section 18.7). We have seen that when a substrate is oxidized by NAD^+, the substrate donates a hydride ion to the 4-position of the pyridinium ring (Section 18.7).

oxidation of substrate
reduction of the coenzyme

The product of the two-step reaction sequence, dihydroxyacetone phosphate, is one of the intermediates in glycolysis, so it can enter that pathway directly and be broken down further (Section 19.5).

Now, we will see how fatty acids, the other products formed from the hydrolysis of fats, are metabolized. Before a fatty acid can be metabolized, it must be activated. We have seen that a carboxylic acid can be activated in a cell by first being converted to an

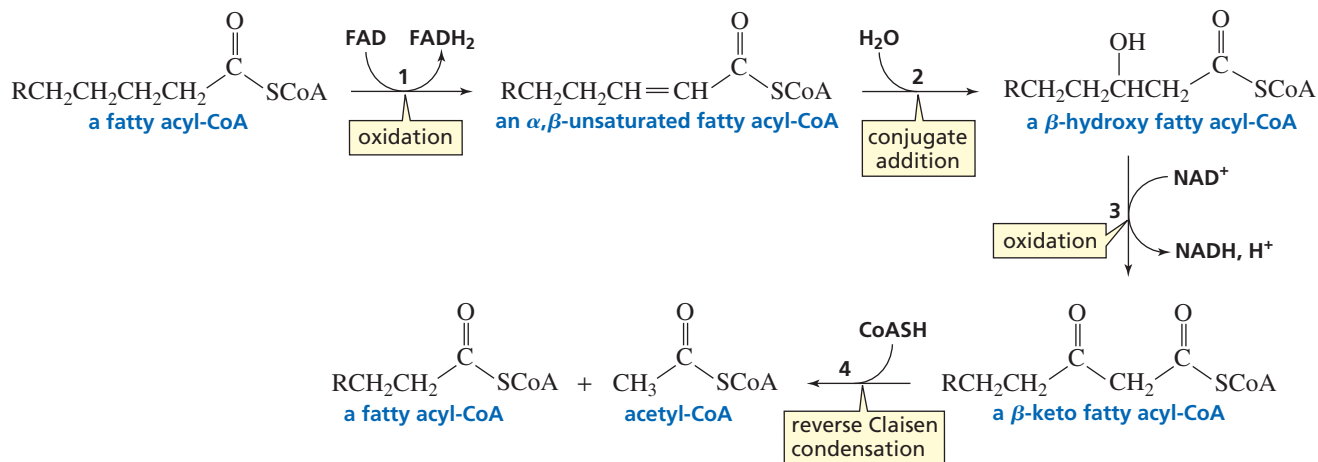
acyl adenylate, which occurs when the carboxylate ion attacks the α-phosphorus of ATP. The acyl adenylate then reacts with coenzyme A in a nucleophilic acyl substitution reaction to form a thioester (Section 11.16).

$$\underset{\text{a fatty acid}}{RCH_2C(=O)O^-} \xrightarrow[\text{ATP} \quad \text{PP}_i]{} \underset{\text{an acyl adenylate}}{RCH_2C(=O)OP(=O)(O^-)OAd} \xrightarrow[\text{CoASH} \quad \text{AMP}]{} \underset{\substack{\text{a fatty acyl-CoA} \\ \text{a thioester}}}{RCH_2C(=O)SCoA}$$

The fatty acyl-CoA is converted to acetyl-CoA in a repeating four-step pathway called ***β*-oxidation.** Each passage through this series of four reactions removes two carbons from the fatty acyl-CoA by converting them to acetyl-CoA (Figure 19.2). Each of the four reactions is catalyzed by a different enzyme.

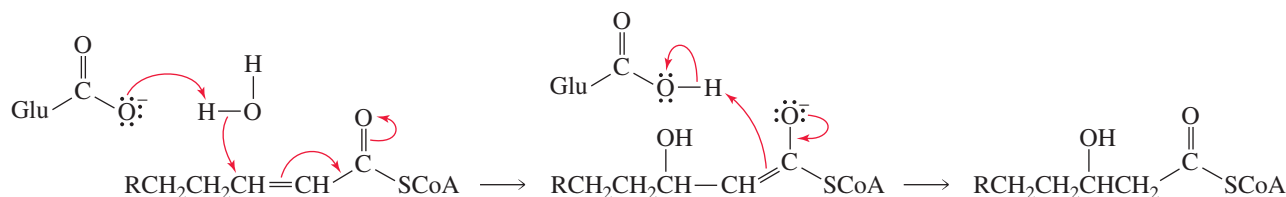
1. The first reaction is an oxidation reaction that removes hydrogens from the α- and β-carbons, forming an α,β-unsaturated fatty acyl-CoA. The oxidizing agent is FAD; the mechanism of this reaction was shown in Section 18.8. The enzyme that catalyzes this reaction has been found to be deficient in 10% of babies that experience sudden infant death syndrome, a condition in which an apparently healthy baby dies, generally while sleeping. Glucose is the cell's primary fuel immediately after a meal, and then the cell switches to a combination of glucose and fatty acids. The inability to oxidize fatty acids may be what causes the infant's distress.

β-Oxidation

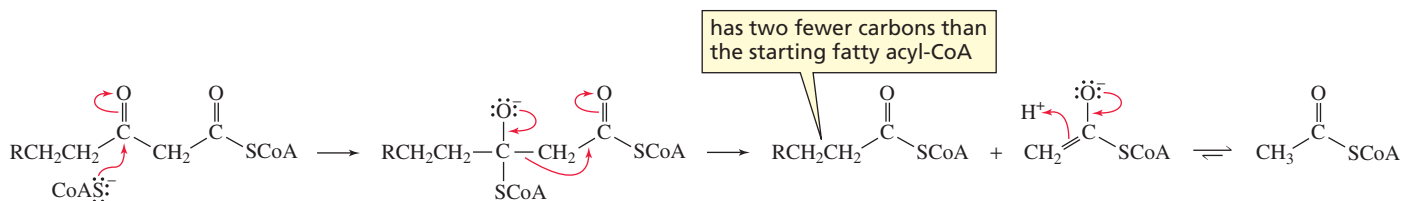
$$\underset{\text{a fatty acyl-CoA}}{RCH_2CH_2CH_2CH_2C(=O)SCoA} \xrightarrow[\text{1 oxidation}]{\text{FAD} \quad \text{FADH}_2} \underset{\text{an } \alpha,\beta\text{-unsaturated fatty acyl-CoA}}{RCH_2CH_2CH{=}CHC(=O)SCoA} \xrightarrow[\text{2 conjugate addition}]{H_2O} \underset{\text{a } \beta\text{-hydroxy fatty acyl-CoA}}{RCH_2CH_2CH(OH)CH_2C(=O)SCoA}$$

$$\xrightarrow[\text{3 oxidation}]{\text{NAD}^+ \quad \text{NADH, H}^+} \underset{\text{a } \beta\text{-keto fatty acyl-CoA}}{RCH_2CH_2C(=O)CH_2C(=O)SCoA} \xrightarrow[\text{4 reverse Claisen condensation}]{\text{CoASH}} \underset{\text{a fatty acyl-CoA}}{RCH_2CH_2C(=O)SCoA} + \underset{\text{acetyl-CoA}}{CH_3C(=O)SCoA}$$

▲ **Figure 19.2**
In β-oxidation, a series of four enzyme-catalyzed reactions is repeated until the entire fatty acyl-CoA molecule has been converted to acetyl-CoA molecules. The enzymes that catalyze the reactions are 1. acyl-CoA dehydrogenase; 2. enoyl-CoA hydratase; 3. 3-L-hydroxyacyl-CoA dehydrogenase; and 4. β-ketoacyl-CoA thiolase.

2. The second reaction, whose mechanism is shown below, is the conjugate addition of water to the α,β-unsaturated fatty acyl-CoA (Section 12.10). A glutamate side chain of the enzyme removes a proton from water, making it a better nucleophile; the enolate ion is protonated by glutamic acid.

$$\text{Glu}C(=O)\ddot{O}^- \;\; H{-}O{-}H \;\; RCH_2CH_2CH{=}CHC(=O)SCoA \longrightarrow \text{Glu}C(=O)\ddot{O}{-}H \;\; RCH_2CH_2CH(OH){-}CH{=}C(\ddot{O}^-)SCoA \longrightarrow RCH_2CH_2CH(OH)CH_2C(=O)SCoA$$

3. The third reaction is another oxidation reaction: NAD^+ oxidizes the secondary alcohol to a ketone. Recall that the mechanism for all NAD^+ oxidations involves donation of a hydride ion from the substrate to the 4-positon of the pyridinium ring of NAD^+ (Section 18.7).
4. The fourth reaction is the reverse of a Claisen condensation (Section 13.8), followed by conversion of the enolate ion to the keto tautomer (Section 13.3). The mechanism for this reaction is shown here. The final product is acetyl-CoA and a fatty acyl-CoA *with two fewer carbons* than the starting fatty acyl-CoA.

has two fewer carbons than the starting fatty acyl-CoA

$RCH_2CH_2C(=O)CH_2C(=O)SCoA$ + $CoAS^-$ ⟶ $RCH_2CH_2-C(O^-)(SCoA)-CH_2C(=O)SCoA$ ⟶ $RCH_2CH_2C(=O)SCoA$ + $CH_2=C(O^-)SCoA$ (+ H^+) ⇌ $CH_3C(=O)SCoA$

Fatty acids are converted to molecules of acetyl-CoA.

The four reactions are repeated, forming another molecule of acetyl-CoA and a fatty acyl-CoA that is now four carbons shorter than it was originally. Each time the series of four reactions is repeated, two more carbons are removed (as acetyl-CoA) from the fatty acyl-CoA. The series of reactions is repeated until the entire fatty acid has been converted into acetyl-CoA molecules. In Section 19.8, we will see how acetyl-CoA enters the citric acid cycle.

PROBLEM 1♦

Palmitic acid is a 16-carbon saturated fatty acid. How many molecules of acetyl-CoA are formed from one molecule of palmitic acid?

PROBLEM 2♦

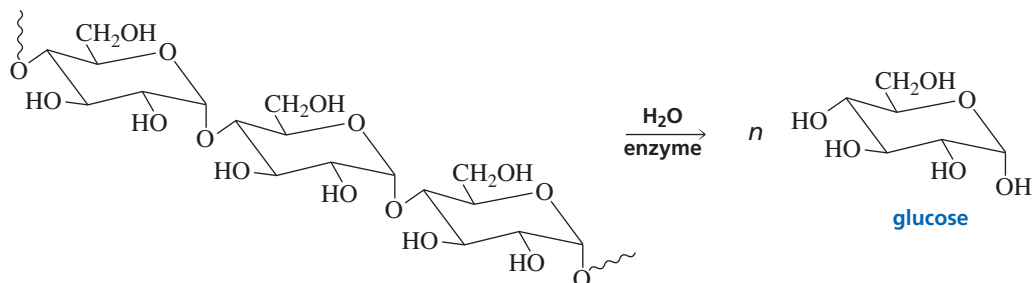
How many molecules of NADH are formed from the β-oxidation of one molecule of palmitic acid?

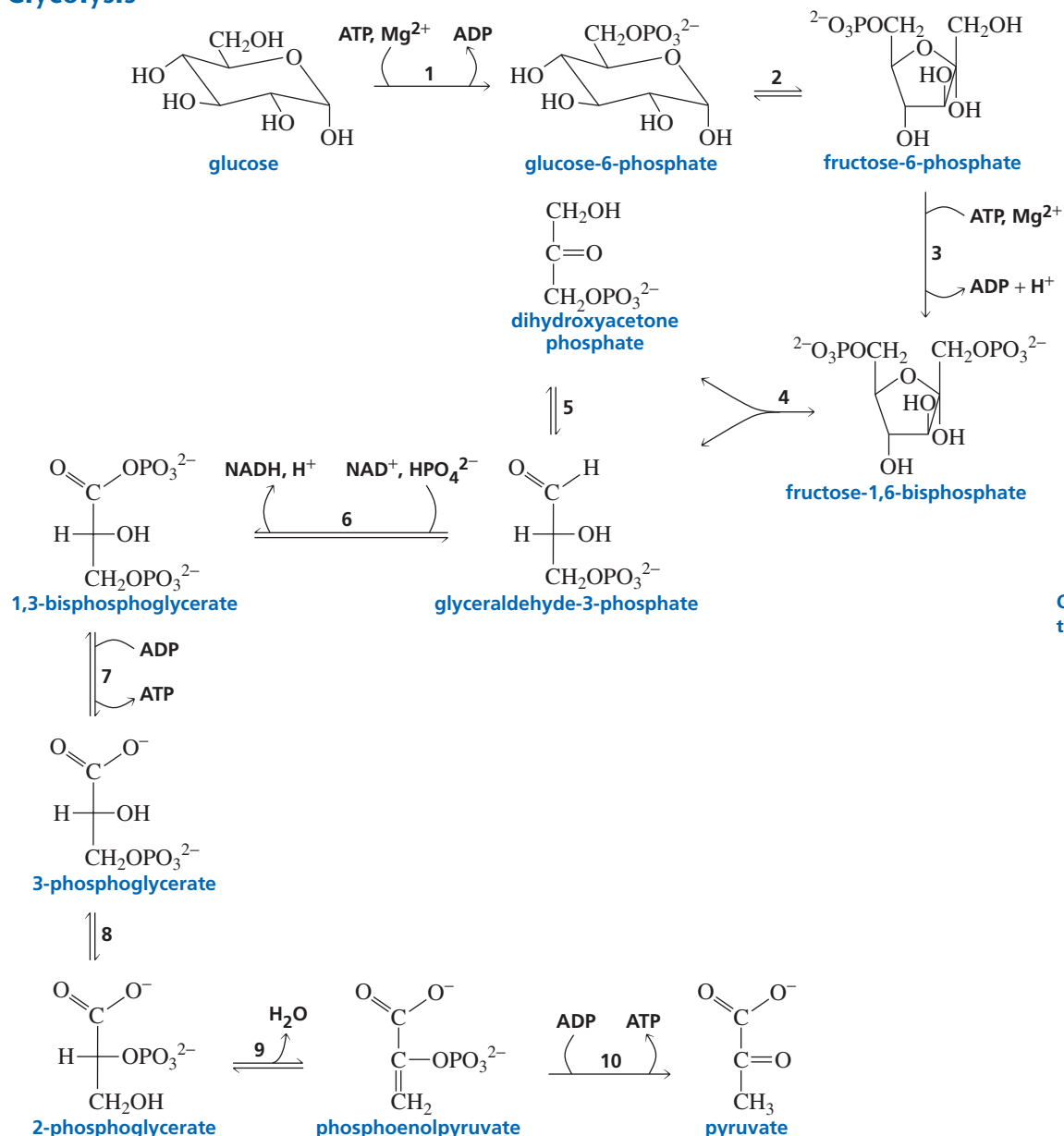
PROBLEM 3♦

Why does the OH group add to the β-carbon rather than to the α-carbon in the second reaction in the β-oxidation of fats? (*Hint:* See Section 12.10.)

19.5 THE CATABOLISM OF CARBOHYDRATES

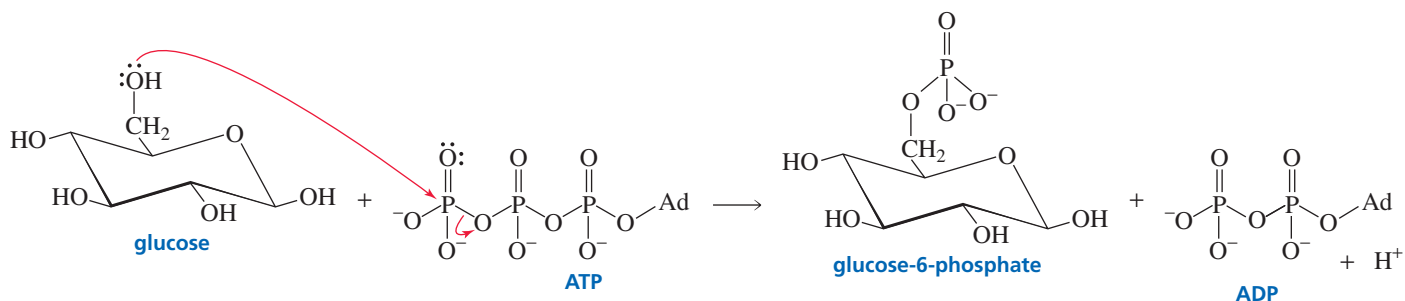
In the first stage of carbohydrate catabolism, the glycosidic bonds that hold glucose subunits together as acetals are hydrolyzed in an enzyme-catalyzed reaction, forming individual glucose molecules (Section 16.10).

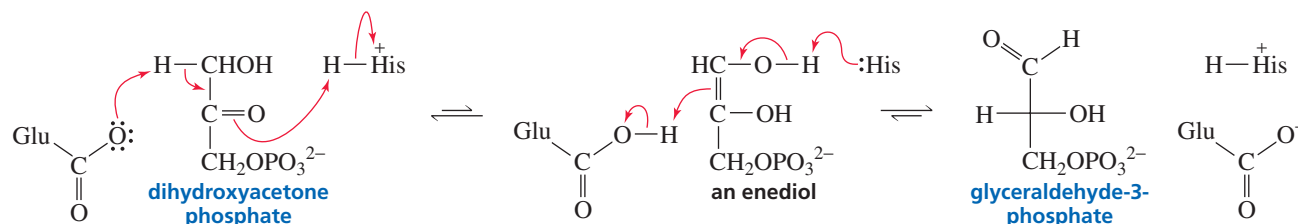
$\xrightarrow[\text{enzyme}]{H_2O}$ *n* glucose

In the second stage of catabolism, each glucose molecule is converted to two molecules of pyruvate in a series of 10 reactions known as **glycolysis** or the *glycolytic pathway* (Figure 19.3).

Glycolysis

Glucose is converted to two molecules of pyruvate.

▲ Figure 19.3

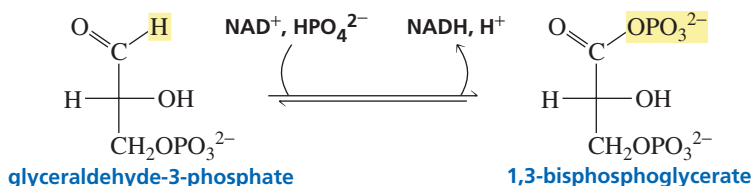
Glycolysis, the series of enzyme-catalyzed reactions responsible for converting 1 mol of glucose to 2 mol of pyruvate. The enzymes that catalyze the reactions are 1. hexokinase; 2. phosphoglucose isomerase; 3. phosphofructokinase; 4. aldolase; 5. triosephosphate isomerase; 6. glyceraldehyde-3-phosphate dehydrogenase; 7. phosphoglycerate kinase; 8. phosphoglycerate mutase; 9. enolase; and 10. pyruvate kinase.

1. In the first reaction, glucose is converted to glucose-6-phosphate by attacking the γ-phosphorus of ATP (Section 19.1).

2. Glucose-6-phosphate then isomerizes to fructose-6-phosphate, a reaction whose mechanism we examined in Section 18.4.
3. In the third reaction, ATP puts a second phosphate group on fructose-6-phosphate, forming fructose-1,6-bisphosphate. The mechanism of this reaction is the same as the one that converts glucose to glucose-6-phosphate.
4. The fourth reaction is the reverse of an aldol addition. We looked at the mechanism of this reaction in Section 18.5.
5. Dihydroxyacetone phosphate, produced in the fourth reaction, forms an enediol that then forms glyceraldehyde-3-phosphate (if the OH group at C-1 is the one that ketonizes) or reforms dihydroxyacetone phosphate (if the OH group at C-2 is the one that ketonizes).

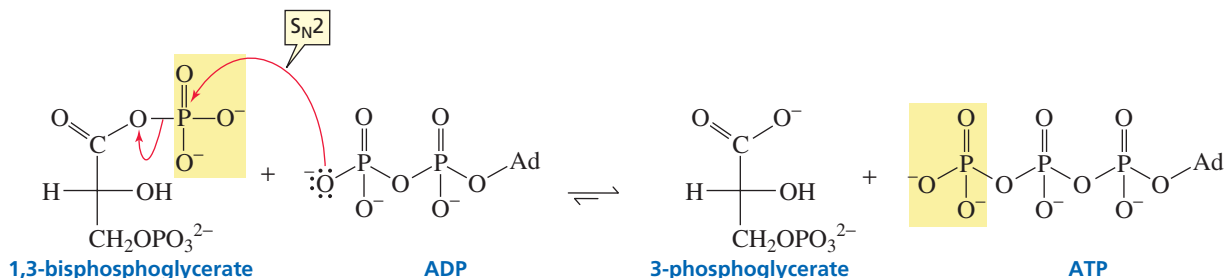
dihydroxyacetone phosphate ⇌ an enediol ⇌ glyceraldehyde-3-phosphate

The mechanism of this reaction shows that a glutamate side chain of the enzyme removes a proton from the α-carbon, and a protonated histidine side chain donates a proton to the carbonyl oxygen. In the next step, the histidine removes a proton from the C-1 OH group, and glutamic acid protonates C-2. Compare this mechanism with the one for the enediol rearrangement in Section 16.5.

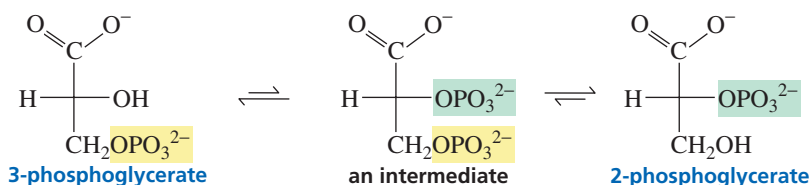
Because each molecule of glucose is converted to a molecule of glyceraldehyde-3-phosphate *and* a molecule of dihydroxyacetone phosphate, and each molecule of dihydroxyacetone phosphate is converted to glyceraldehyde-3-phosphate, then overall each molecule of glucose is converted to two molecules of glyceraldehyde-3-phosphate.

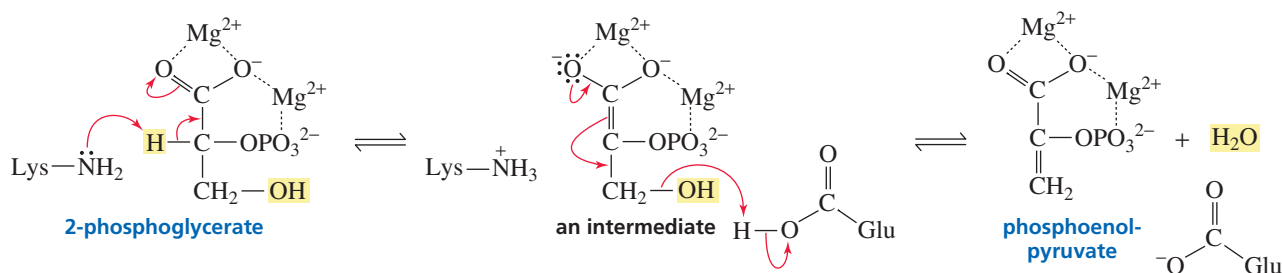
6. The aldehyde group of glyceraldehyde-3-phosphate is oxidized by NAD^+, forming 1,3-bisphosphoglycerate. In this reaction, the aldehyde is oxidized to a carboxylic acid, which then forms an ester with phosphoric acid. We looked at the mechanism of this reaction in Section 18.7.

glyceraldehyde-3-phosphate ⇌ (NAD^+, HPO_4^{2-} → NADH, H^+) 1,3-bisphosphoglycerate

7. In the seventh reaction, a phosphate group is transferred from 1,3-bisphosphoglycerate to ADP by breaking an anhydride bond.

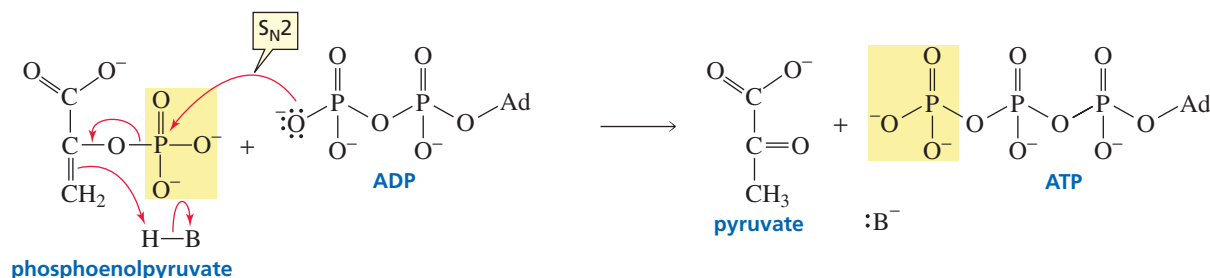
S_N2

1,3-bisphosphoglycerate + ADP ⇌ 3-phosphoglycerate + ATP

8. The eighth reaction is an isomerization in which 3-phosphoglycerate is converted to 2-phosphoglycerate. The enzyme that catalyzes this reaction has a phosphate group attached to a side chain that it transfers to the 2-position of 3-phosphoglycerate to form an intermediate with two phosphate groups. The intermediate transfers the phosphate group on its 3-position back to the side chain of the enzyme.

3-phosphoglycerate ⇌ an intermediate ⇌ 2-phosphoglycerate

9. The ninth reaction is a dehydration reaction that forms phosphoenolpyruvate. A lysine side chain removes a proton from the α-carbon. Two magnesium ions increase the acidity of the proton by stabilizing the conjugate base. The HO group of the intermediate is protonated by a glutamic acid side chain, which makes the OH group a better leaving group (Section 9.2).

2-phosphoglycerate ⇌ an intermediate ⇌ phosphoenolpyruvate + H_2O

10. In the last reaction, phosphoenolpyruvate transfers its phosphate group to ADP, forming pyruvate and ATP.

S_N2

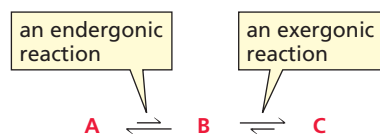
phosphoenolpyruvate + ADP ⟶ pyruvate + ATP

Phosphorylating glucose in the first reaction of glycolysis and phosphorylating fructose-6-phosphate in the third reaction do not make glucose or fructose-6-phosphate any more reactive. The purpose of phosphorylation is to put a group on each of those compounds that allows enzymes to recognize them (and recognize the subsequent intermediates formed in glycolysis) so that they can be bound at their active site. The two molecules of ATP that are used to put these "handles" on the sugar molecules are re-formed in the last step of glycolysis—namely, in the conversion of two molecules of phosphoenolpyruvate to two molecules of pyruvate and two molecules of ATP.

Glycolysis is exergonic overall, but all the reactions in the pathway are not themselves exergonic. For example, the conversion of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate (the sixth reaction; A to B as shown below) is an endergonic reaction. However, the subsequent reaction (the conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate; B to C as shown below) is highly exergonic. Therefore, as the second reaction converts B to C, the first reaction will replenish the equilibrium concentration of B. Recall that an endergonic reaction followed by an exergonic reaction are called **coupled reactions** (Section 5.5).

an endergonic reaction

an exergonic reaction

A ⇌ B ⇌ C

PROBLEM 4

Draw the mechanism for the third reaction in glycolysis—the reaction of fructose-6-phosphate with ATP to form fructose-1,6-bisphosphate.

PROBLEM 5♦

a. Which steps in glycolysis consume ATP? **b.** Which steps in glycolysis produce ATP?

PROBLEM 6

The oxidation of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate is an endergonic reaction, but the flow through this point in glycolysis proceeds smoothly. How is the unfavorable equilibrium constant overcome?

PROBLEM-SOLVING STRATEGY

Calculating Production of ATP

How many molecules of ATP are obtained from each molecule of glucose that is metabolized to pyruvate?

First, we need to count the number of ATPs used to convert glucose to pyruvate. We see that two are used: one to form glucose-6-phosphate and the other to form fructose-1,6-bisphosphate.

Next, we need to know many ATPs are formed. Each glyceraldehyde-3-phosphate that is metabolized to pyruvate forms two ATPs. Because each molecule of glucose forms two molecules of glyceraldehyde-3-phosphate, four molecules of ATP are formed from each molecule of glucose. Subtracting the two molecules used, we find that each molecule of glucose that is metabolized to pyruvate forms two molecules of ATP.

Now continue on to Problem 7.

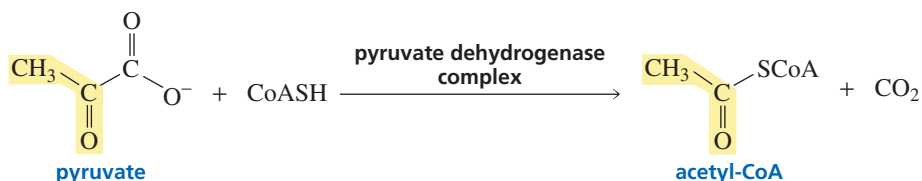
PROBLEM 7♦

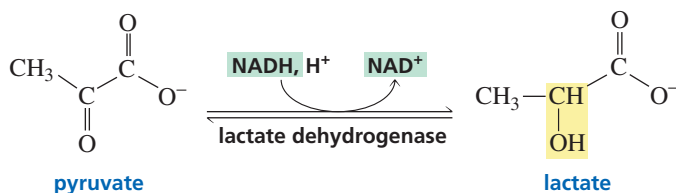
How many molecules of NAD^+ are required to convert one molecule of glucose to pyruvate?

19.6 THE FATE OF PYRUVATE

We have just seen that NAD^+, which cells have in limited supply, is used as an oxidizing agent in glycolysis. If glycolysis is to continue, the NADH that is produced must to be oxidized back to NAD^+. Otherwise, no NAD^+ will be available as an oxidizing agent.

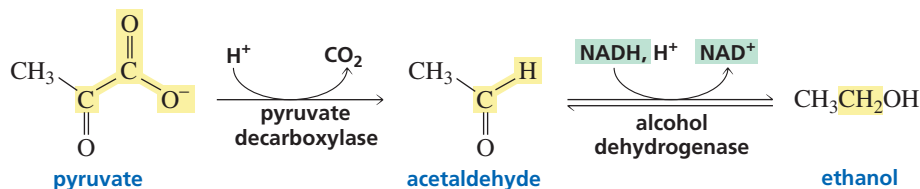
Under normal (aerobic) conditions (that is, when oxygen is present), oxygen oxidizes NADH back to NAD^+ (this happens in *the fourth stage of catabolism*), and pyruvate (the product of glycolysis) is converted to acetyl-CoA, which then enters the citric acid cycle.

The conversion of pyruvate to acetyl-CoA occurs via a series of reactions catalyzed by a complex of three enzymes and five coenzymes, known collectively as the pyruvate dehydrogenase complex. The overall result of this series of reactions is to transfer the acetyl group of pyruvate to coenzyme A (CoASH). We looked at the mechanisms for this series of reactions in Section 18.9.

When oxygen is in short supply, such as when intense activity depletes much of the oxygen in muscle cells, pyruvate (the product of glycolysis) oxidizes NADH back to NAD^+. In the process, pyruvate is reduced to lactate (lactic acid). The need to replenish oxygen is why people breathe hard during exercise.

$$CH_3C(=O)COO^- \xrightarrow[\text{lactate dehydrogenase}]{\text{NADH, H}^+ \;\; \text{NAD}^+} CH_3CH(OH)COO^-$$

pyruvate → lactate

Although pyruvate is reduced to lactate under anaerobic (oxygen-free) conditions in animals, it has a different fate in yeast—namely, it is decarboxylated to acetaldehyde by pyruvate decarboxylase (an enzyme that is not present in animals). We looked at the mechanism of this reaction in Section 18.10.

$$CH_3C(=O)COO^- \xrightarrow[\text{pyruvate decarboxylase}]{H^+ \;\; CO_2} CH_3CHO \xrightarrow[\text{alcohol dehydrogenase}]{\text{NADH, H}^+ \;\; \text{NAD}^+} CH_3CH_2OH$$

pyruvate → acetaldehyde → ethanol

In this case, acetaldehyde is the compound that oxidizes NADH back to NAD^+ and in the process is reduced to ethanol. This reaction has been used by humankind for thousands of years to produce wine, beer, and other fermented drinks. (Notice that enzyme names can refer either to the forward or to the reverse reaction. For example, pyruvate decarboxylase refers to the forward reaction, whereas alcohol dehydrogenase refers to the reverse reaction.)

PROBLEM 8♦

Suggest a name for alcohol dehydrogenase that would refer to the forward reaction—that is, to the conversion of acetaldehyde to ethanol.

PROBLEM 9♦

What functional group of pyruvate is reduced when pyruvate is converted to lactate?

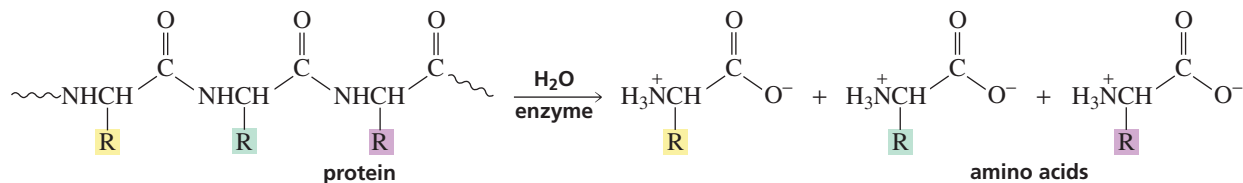
PROBLEM 10

Propose a mechanism for the reduction of acetaldehyde by NADH to ethanol. (*Hint:* See Section 18.1.)

19.7 THE CATABOLISM OF PROTEINS

In the first stage of protein catabolism, proteins are hydrolyzed in an enzyme-catalyzed reaction to amino acids.

$$\sim\sim NHCH(R)C(=O)NHCH(R)C(=O)NHCH(R)C(=O)\sim\sim \xrightarrow[\text{enzyme}]{H_2O} H_3\overset{+}{N}CH(R)COO^- + H_3\overset{+}{N}CH(R)COO^- + H_3\overset{+}{N}CH(R)COO^-$$

protein → amino acids

In the second stage of catabolism, the amino acids are converted to acetyl-CoA, pyruvate, and/or citric acid cycle intermediates, depending on the amino acid. The products of the second stage of catabolism then enter the citric acid cycle—the third stage of catabolism—and are further metabolized.

Amino acids are converted to acetyl-CoA, pyruvate, and/or citric acid cycle intermediates.

We will use the catabolism of phenylalanine as an example of how an amino acid is metabolized (Figure 19.4). Phenylalanine is one of the essential amino acids, so it must be included in our diet (Section 17.1). The enzyme phenylalanine hydroxylase converts phenylalanine to tyrosine. Thus, tyrosine is not an essential amino acid, unless the diet lacks phenylalanine.

The first reaction in the catabolism of most amino acids is transamination, a reaction that requires the coenzyme pyridoxal phosphate (PLP). We saw that transamination replaces the amino group of the amino acid with a ketone group (Section 18.11). *para*-Hydroxyphenylpyruvate, the product of the transamination of tyrosine, is converted by a series of reactions to fumarate and acetyl-CoA.

phenylalanine hydroxylase

phenylalanine

tyrosine

tyrosine aminotransferase

PLP

para-hydroxyphenylpyruvate

noradrenaline

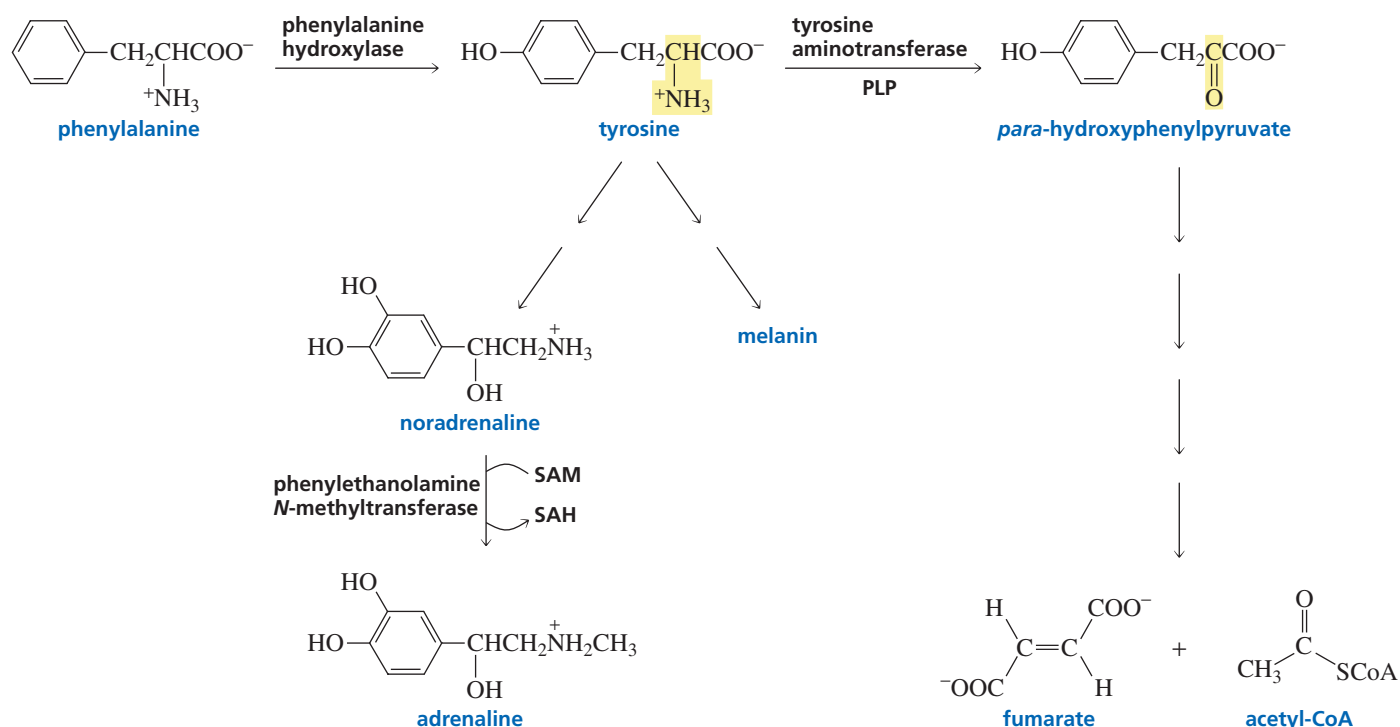
melanin

phenylethanolamine *N*-methyltransferase

SAM

SAH

adrenaline

fumarate

acetyl-CoA

▲ **Figure 19.4**
The catabolism of phenylalanine.

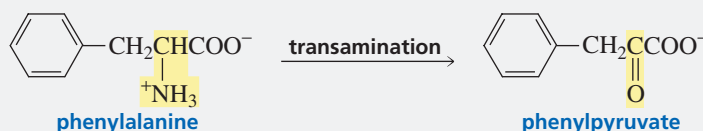
Fumarate is a citric acid cycle intermediate, so it can enter the citric acid cycle directly. We will see in Section 19.8 that acetyl-CoA is the only non-citric-acid-cycle intermediate that can enter the citric acid cycle. Remember that each of the reactions in this catabolic pathway is catalyzed by a different enzyme.

In addition to being used for energy, the amino acids that we ingest are also used for the synthesis of proteins and for the synthesis of other compounds the body needs. For example, tyrosine is used to synthesize neurotransmitters (noradrenaline and adrenaline) and melanin, which is the compound responsible for skin and hair pigmentation. Recall that *S*-adenosylmethionine (SAM) is the biological methylating agent that converts noradrenaline to adrenaline (Section 9.12).

Phenylketonuria (PKU): An Inborn Error of Metabolism

About one in every 20,000 babies is born without phenylalanine hydroxylase, the enzyme that converts phenylalanine to tyrosine. This genetic disease is called phenylketonuria (PKU). Without phenylalanine hydroxylase, the level of phenylalanine builds up; when it reaches a high concentration, it is transaminated to phenylpyruvate, a compound that interferes with normal brain development. The high level of phenylpyruvate found in urine gives the disease its name.

$$C_6H_5-CH_2CH(^+NH_3)COO^- \xrightarrow{\text{transamination}} C_6H_5-CH_2C(=O)COO^-$$

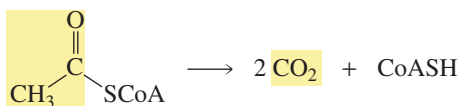
phenylalanine → phenylpyruvate

Within 24 hours after birth, all babies born in the United States are tested for high serum phenylalanine levels, which indicate a buildup of phenylalanine caused by the absence of phenylalanine hydroxylase. Babies with high levels are immediately put on a diet low in phenylalanine and high in tyrosine. As long as the phenylalanine level is kept under careful control for the first 5 to 10 years of life, the child will experience no adverse effects. You may have noticed the warning on containers of foods that contain NutraSweet, announcing that it contains phenylalanine. (Recall that this sweetener is a methyl ester of a dipeptide of L-aspartate and L-phenylalanine; see page 591).

If phenylalanine in the diet is not controlled, then the baby will be severely mentally retarded by the time he or she is a few months old. Untreated children have paler skin and fairer hair than other members of their family because, without tyrosine, they cannot synthesize melanin, a skin and hair pigment. Half of untreated phenylketonurics die by age 20. When a woman with PKU becomes pregnant, she must return to the low-phenylalanine diet she had as a child because a high level of phenylalanine can cause abnormal development of the fetus.

PROBLEM 11♦

What compound is formed when alanine is transaminated?

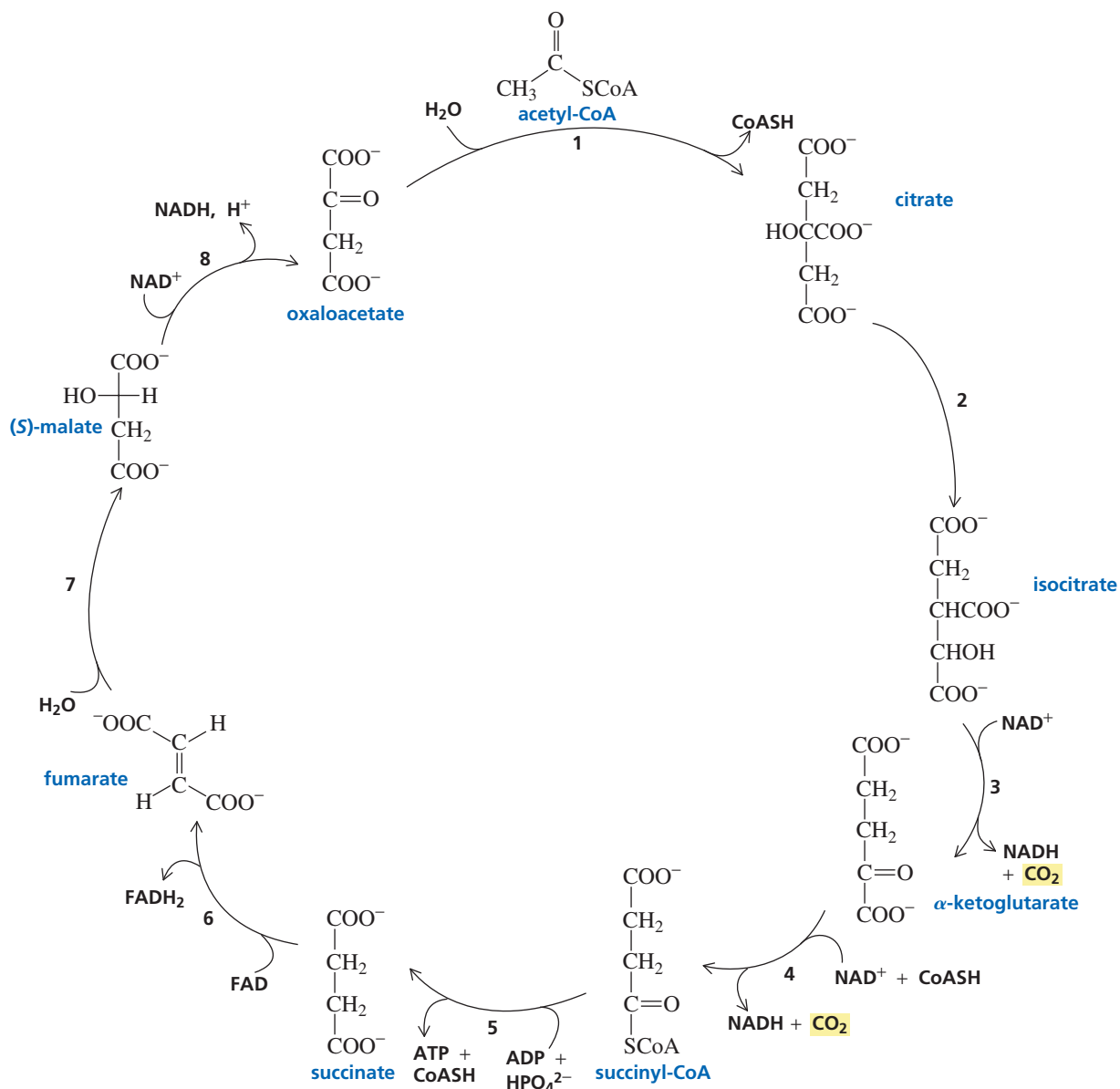
19.8 THE CITRIC ACID CYCLE

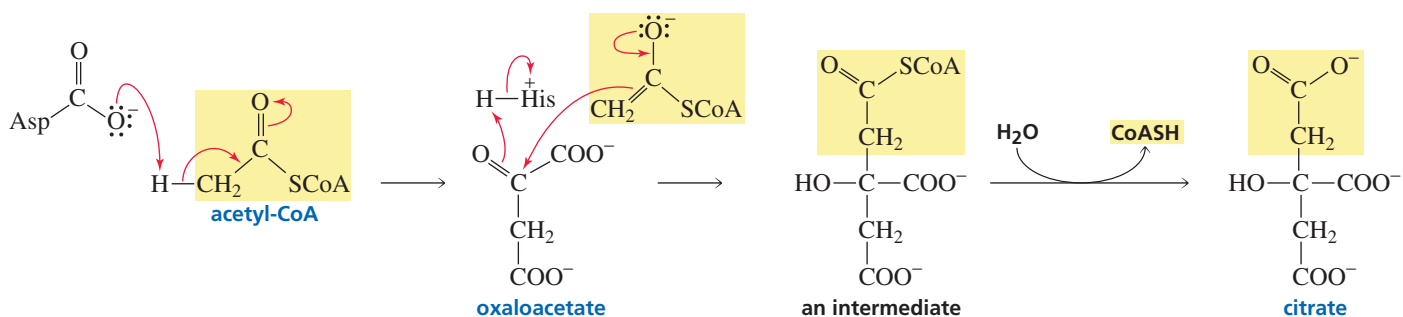
The **citric acid cycle** (third stage of catabolism) is a series of eight reactions in which the acetyl group of each molecule of acetyl-CoA—formed by the catabolism of fats, carbohydrates, and amino acids—is converted to two molecules of CO_2 (Figure 19.5).

$$CH_3C(=O)SCoA \longrightarrow 2\,CO_2 + CoASH$$

The acetyl group of each molecule of acetyl-CoA that enters the citric acid cycle is converted to two molecules of CO_2.

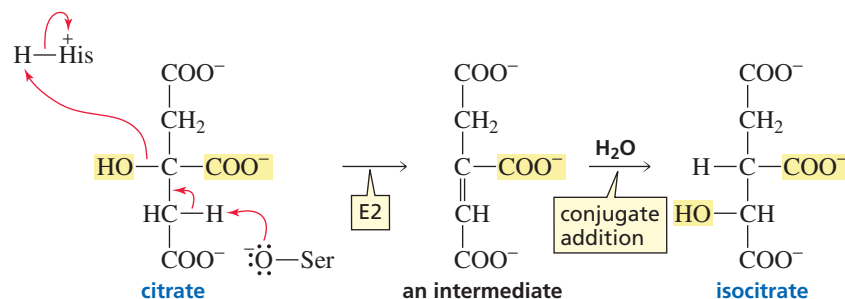
The series of reactions is called a *cycle* because, unlike the reactions of other metabolic pathways, they comprise a closed loop in which the product of the eighth reaction (oxaloacetate) is the reactant for the first reaction.

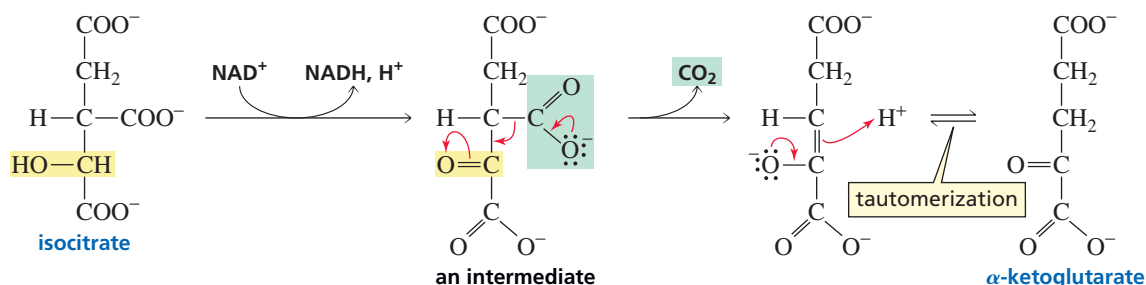
1. In the first reaction of the citric acid cycle, acetyl-CoA reacts with oxaloacetate to form citrate. The mechanism of the reaction shows that an aspartate side chain of the enzyme removes a proton from the α-carbon of acetyl-CoA, creating an enolate ion. This enolate ion adds to the keto carbonyl carbon of oxaloacetate and the carbonyl oxygen picks up a proton from a histidine side chain. This is similar to an *aldol addition* in which the α-carbanion (enolate ion) of one molecule is the nucleophile and the carbonyl carbon of another is the electrophile (Section 13.5). The intermediate (a thioester) that results is hydrolyzed to citrate in a *nucleophilic acyl substitution* reaction (Section 11.7).

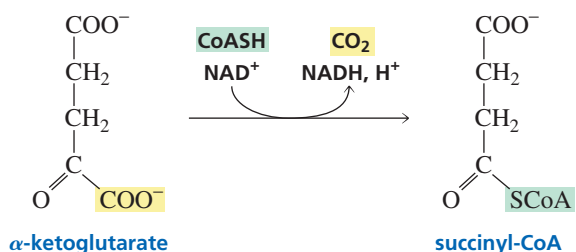
The Citric Acid Cycle

▲ **Figure 19.5**

The citric acid cycle is the series of enzyme-catalyzed reactions responsible for the oxidation of the acetyl group of acetyl-CoA to two molecules of CO_2. The enzymes that catalyze the reactions are: 1. citrate synthase; 2. aconitase; 3. isocitrate dehydrogenase; 4. α-ketoglutarate dehydrogenase; 5. succinyl-CoA synthetase; 6. succinate dehydrogenase; 7. fumarase; and 8. malate dehydrogenase.

2. In the second reaction, citrate is converted to isocitrate, its isomer. The reaction takes place in two steps: water is removed in the first step and then re-added in the second step. The first step is an *E2 dehydration* (Section 9.4) in which a serine side chain

removes a proton, and the OH leaving group is protonated by a histidine side chain to make it a weaker base (H_2O) and, therefore, a better leaving group. In the second step, *conjugate addition* of water to the intermediate forms isocitrate (Section 12.10).

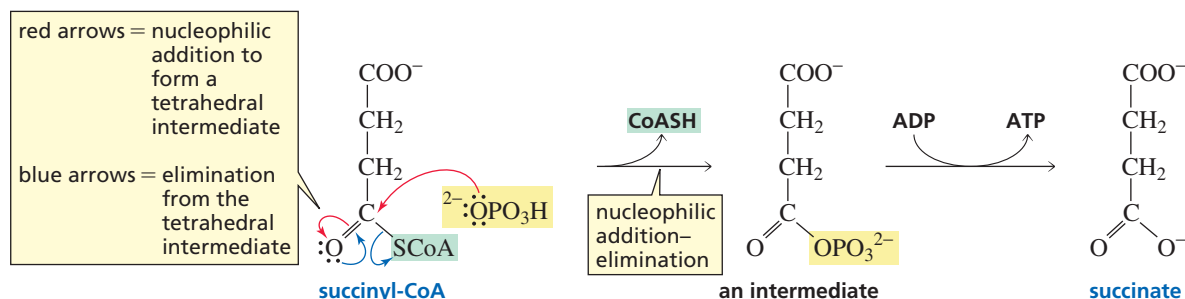
citrate → (E2) → an intermediate → (H_2O, conjugate addition) → isocitrate

3. The third reaction is the one that releases the first molecule of CO_2. It also has two steps. In the first, the secondary alcohol group of isocitrate is *oxidized* to a ketone by NAD^+ (Section 18.7). In the second, the ketone *loses* CO_2. We have seen that a CO_2 group bonded to a carbon that is adjacent to a carbonyl carbon can be removed because the electrons left behind can be delocalized onto the carbonyl oxygen (Section 13.9). The enolate ion tautomerizes to a ketone (Section 13.3).

isocitrate → (NAD^+ → NADH, H^+) → an intermediate → (CO_2) → (tautomerization) → α-ketoglutarate

4. The fourth reaction is the one that releases the second molecule of CO_2. The reaction requires a group of enzymes (with the same mechanisms) and the same five coenzymes required by the pyruvate dehydrogenase complex that forms acetyl-CoA (Section 18.9). Like the reaction catalyzed by the pyruvate dehydrogenase complex, the overall result of this reaction is the *transfer of an acyl group to CoASH*. Thus, the product of the reaction is succinyl-CoA.

α-ketoglutarate → (CoASH, NAD^+ → CO_2, NADH, H^+) → succinyl-CoA

5. The fifth reaction takes place in two steps. First, hydrogen phosphate reacts with succinyl-CoA in a *nucleophilic acyl substitution* reaction to form an intermediate, which then transfers its phosphate group to ADP, using the same mechanism as used in steps 7 and 10 of glycolysis.

red arrows = nucleophilic addition to form a tetrahedral intermediate

blue arrows = elimination from the tetrahedral intermediate

succinyl-CoA + $^{2-}$:ÖPO$_3$H → (nucleophilic addition–elimination; CoASH) → an intermediate → (ADP → ATP) → succinate

At this point, the citric acid cycle has accomplished the required transformation—that is, acetyl-CoA has been converted to CoASH and two molecules of CO_2. What remains to be done is to convert succinate to oxaloacetate, so oxaloacetate can begin the cycle again by reacting with another molecule of acetyl-CoA.

6. In the sixth reaction, FAD *oxidizes* succinate to fumarate. We looked at the mechanism of this reaction in Section 18.8.
7. *Conjugate addition* of water to the double bond of fumarate forms (*S*)-malate. We saw why the reaction forms only one enantiomer in Section 6.7.
8. *Oxidation* of the secondary alcohol group of (*S*)-malate by NAD^+ forms oxaloacetate, returning the cycle to its starting point. Oxaloacetate now begins the cycle again, reacting with another molecule of acetyl-CoA to initiate the conversion of acetyl-CoA's acetyl group to another two molecules of CO_2.

Notice that reactions 6, 7, and 8 in the citric acid cycle are similar to reactions 1, 2, and 3 in the β-oxidation of fatty acids (Section 19.4).

PROBLEM 12

Acid-catalyzed dehydration reactions are normally E1 reactions. Why is the acid-catalyzed dehydration in the second reaction of the citric acid cycle an E2 reaction?

PROBLEM 13♦

What functional group of isocitrate is oxidized in the third reaction of the citric acid cycle?

PROBLEM 14♦

The citric acid cycle is also called the tricarboxylic acid cycle (or TCA cycle). Which of the citric acid cycle intermediates are tricarboxylic acids?

PROBLEM 15♦

What acyl group is transferred by thiamine pyrophosphate in the fourth reaction of the citric acid cycle? (*Hint:* see Section 18.9.)

19.9 OXIDATIVE PHOSPHORYLATION

The NADH and $FADH_2$ molecules formed in the second and third stages of catabolism undergo **oxidative phosphorylation**—the fourth stage of catabolism—which oxidizes them back to NAD^+ and FAD so that they can participate in more oxidation reactions.

CH_3O, CH_3O, O, O, H, CH_3, 10

coenzyme Q_{10}

The electrons lost when NADH and $FADH_2$ are oxidized are transferred to a system of linked electron acceptors. One of the first electron acceptors is coenzyme Q_{10}, which is a quinone. We have seen that when a quinone gains electrons (is reduced), it forms a hydroquinone (Section 14.7). When hydroquinone passes electrons to the next electron acceptor, hydroquinone is oxidized back to quinone. The last electron acceptor is O_2. When O_2 accepts electrons, it is eventually reduced to water. This chain of oxidation–reduction reactions supplies the energy that is used to convert ADP to ATP.

For each NADH that undergoes oxidative phosphorylation, 2.5 molecules of ATP are formed, and for each $FADH_2$ that undergoes oxidative phosphorylation, 1.5 molecules of ATP are formed.

In oxidative phosphorylation, each molecule of NADH forms 2.5 molecules of ATP and each molecule of $FADH_2$ forms 1.5 molecules of ATP.

$$\text{NADH} \longrightarrow \text{NAD}^+ + 2.5\ \text{ATP}$$

$$\text{FADH}_2 \longrightarrow \text{FAD} + 1.5\ \text{ATP}$$

Each round of the citric acid cycle forms 3 molecules of NADH, 1 molecule of $FADH_2$, and 1 molecule of ATP. Therefore, for every molecule of acetyl-CoA that enters the citric acid cycle, 10 molecules of ATP are formed: 7.5 molecules from NADH, 1.5 molecules from $FADH_2$, and 1 molecule that is formed in the citric acid cycle.

$$3\ \text{NADH} + \text{FADH}_2 \longrightarrow 3\ \text{NAD}^+ + \text{FAD} + 10\ \text{ATP}$$

Basal Metabolic Rate

Your basal metabolic rate (BMR) is the number of calories you would burn if you stayed in bed all day. A BMR is affected by gender, age, and genetics: it is greater for men than for women, it is greater for young people than for old people, and some people are born with a faster metabolic rate than others. The BMR is also affected by the percentage of body fat: the higher the percentage, the lower the BMR. For humans, the average BMR is about 1600 kcal/day.

In addition to consuming sufficient calories to sustain your basal metabolism, you must also consume calories for the energy needed to carry out physical activities. The more active you are, the more calories you must consume in order to maintain your current weight. People who consume more calories than required by their BMR plus their level of physical activity will gain weight; if they consume fewer calories, they will lose weight.

PROBLEM 16♦

How many molecules of ATP are obtained from the conversion of one molecule of glycerol to pyruvate

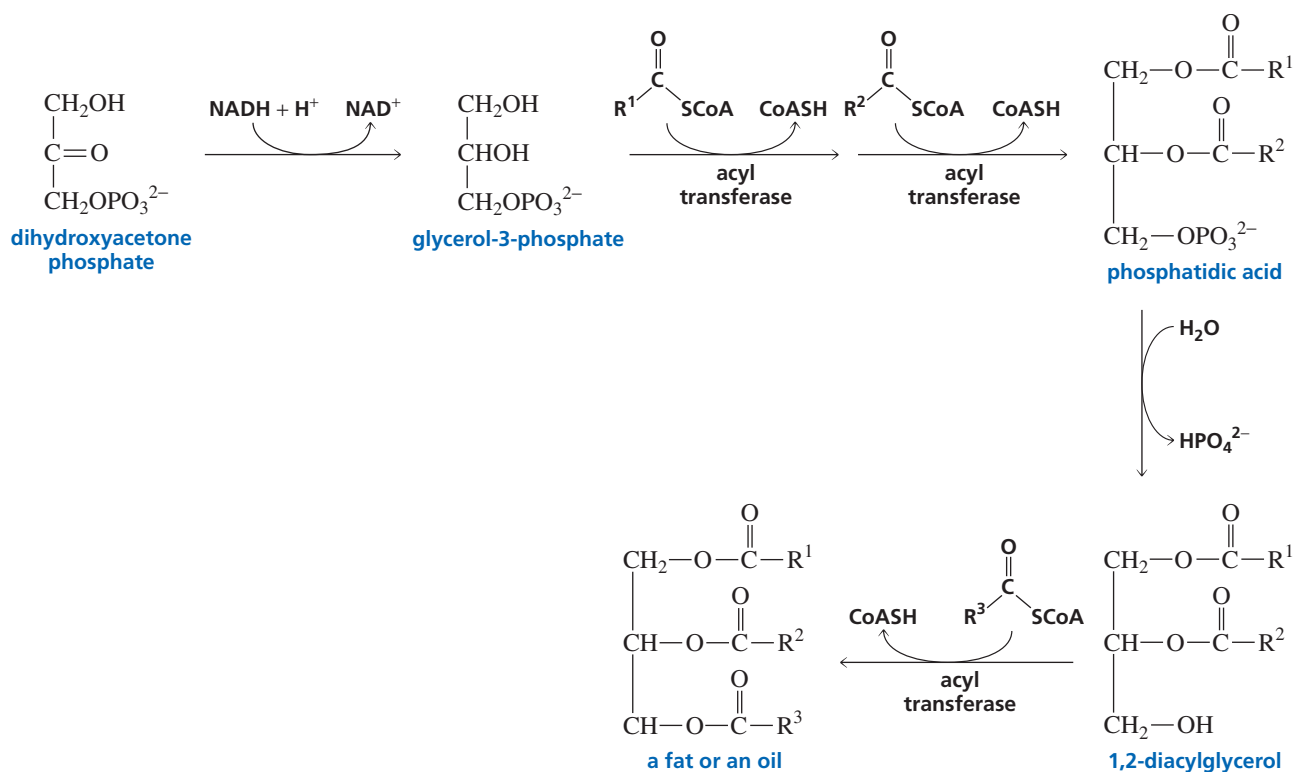
a. not including the fourth stage of catabolism?
b. including the fourth stage of catabolism?

19.10 ANABOLISM

Anabolism is the reverse of catabolism. In anabolism, acetyl-CoA, pyruvate, citric acid cycle intermediates, and intermediates formed in glycolysis are the starting materials for the synthesis of fatty acids, carbohydrates, and proteins.

For example, we have seen how cells use acetyl-CoA to synthesize fatty acyl-CoAs (Section 13.10). Once the fatty acyl-CoAs are synthesized, they can form fats or oils by esterifying glycerol-3-phosphate, which is obtained by reducing dihydroxyacetone phosphate, an intermediate formed in glycolysis.

$$\underset{\text{dihydroxyacetone phosphate}}{CH_2OH-C(=O)-CH_2OPO_3^{2-}} \xrightarrow{NADH + H^+ \rightarrow NAD^+} \underset{\text{glycerol-3-phosphate}}{CH_2OH-CHOH-CH_2OPO_3^{2-}} \xrightarrow[\text{acyl transferase}]{R^1C(=O)SCoA \rightarrow CoASH} \xrightarrow[\text{acyl transferase}]{R^2C(=O)SCoA \rightarrow CoASH} \underset{\text{phosphatidic acid}}{CH_2-O-C(=O)-R^1,\ CH-O-C(=O)-R^2,\ CH_2-OPO_3^{2-}}$$

$$\xrightarrow{H_2O \rightarrow HPO_4^{2-}} \underset{\text{1,2-diacylglycerol}}{CH_2-O-C(=O)-R^1,\ CH-O-C(=O)-R^2,\ CH_2-OH} \xrightarrow[\text{acyl transferase}]{R^3C(=O)SCoA \rightarrow CoASH} \underset{\text{a fat or an oil}}{CH_2-O-C(=O)-R^1,\ CH-O-C(=O)-R^2,\ CH-O-C(=O)-R^3}$$

PROBLEM 17♦

a. What is the name of the enzyme that converts glycerol to glycerol-3-phosphate?
b. What is the name of the enzyme that converts phosphatidic acid to 1,2-diacylglycerol?

19.11 GLUCONEOGENESIS

glycolysis =
glucose → to pyruvate

gluconeogenesis =
pyruvate → glucose

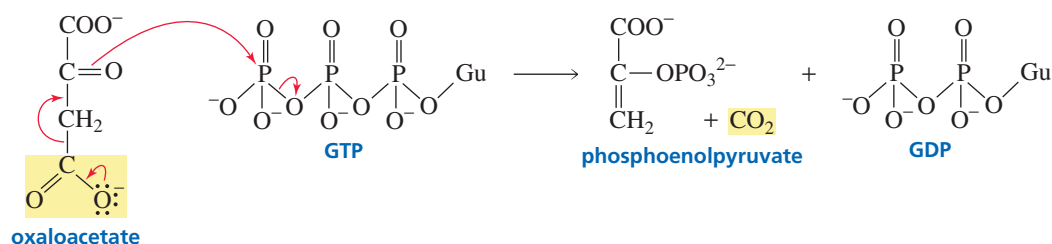
Gluconeogenesis—the synthesis of glucose from pyruvate—is an anabolic pathway. Glucose is the primary fuel for the body. But in times of prolonged exercise or fasting, the body runs out of glucose and has to use fat for its fuel. The brain, however, cannot metabolize fat, so it has to have a continuous supply of glucose. Therefore, the body needs to have a way to synthesize glucose when a sufficient supply is not available.

As you can see by comparing Figures 19.3 and 19.6, many of the reactions involved in the synthesis of glucose are carried out by the same enzymes that catalyze the breakdown

▲ **Figure 19.6**
Glycolysis (the conversion of glucose to pyruvate) and gluconeogenesis (the biosynthesis of glucose from pyruvate).

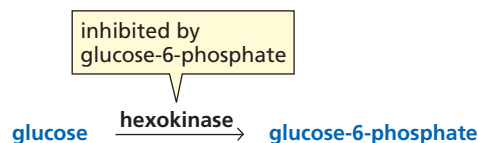
of glucose to pyruvate in glycolysis—they are just operating in reverse. However, all the reactions in gluconeogenesis cannot be just the reverse of those operating in glycolysis. Some of the enzymes in each pathway catalyze essentially irreversible reactions, and detours have to be made around these reactions when going in the other direction. By the use of different enzymes for the forward and reverse irreversible reactions, both pathways become thermodynamically favorable.

Reactions 1, 3, and 10 in glycolysis are irreversible (Figure 19.6). Therefore, a different enzyme is needed to catalyze the reverse of these reactions in gluconeogenesis. The reverse of the last irreversible reaction (10) in glycolysis is actually two successive enzyme-catalyzed reactions. First, pyruvate is converted to oxaloacetate by pyruvate carboxylase, a biotin-dependent enzyme whose mechanism we looked at in Section 18.10. Oxaloacetate is then converted to phosphoenolpyruvate. In this reaction, the 3-oxocarboxylic acid is decarboxylated (Section 13.9) and the oxygen of the enolate ion attacks the γ-phosphorus of GTP as shown below.

oxaloacetate + GTP ⟶ phosphoenolpyruvate + CO_2 + GDP

The hydrolysis of fructose-1,6-bisphosphate to fructose-6-phosphate, the next reaction in gluconeogenesis that needs an enzyme (3) because the reverse reaction is irreversible, is catalyzed by fructose-1,6-bisphosphatase. A **phosphatase** is an enzyme that removes a phosphate group. Finally, glucose-6-phosphatase (1) catalyzes the hydrolysis of glucose-6-phosphate to glucose.

19.12 REGULATING METABOLIC PATHWAYS

The simultaneous synthesis and breakdown of glucose would be counterproductive. Therefore, the two pathways must be controlled so that glucose is synthesized and stored when the cell does not need glucose for energy, and glucose is broken down when it is needed for energy. The enzyme that catalyzes an irreversible reaction near the beginning of a pathway is the one that can be turned on and off. This enzyme is called a **regulatory enzyme.** Regulatory enzymes allow independent control over degradation and synthesis in response to a cell's needs. Some of the ways the three irreversible enzymes in glycolysis and the four irreversible enzymes in gluconeogenesis are controlled are quite complicated. Therefore, we will consider only a few of the control mechanisms here.

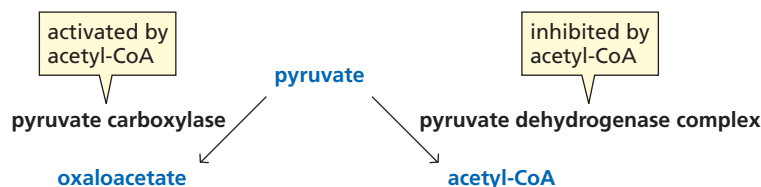
Hexokinase, the first enzyme that catalyzes an irreversible reaction in glycolysis, is a regulatory enzyme. It is inhibited by glucose-6-phosphate, its product. So, if the concentration of glucose-6-phosphate rises above normal levels, then there is no reason to continue to synthesize it, so the enzyme is turned off. Glucose-6-phosphate is a **feedback inhibitor**—that is, it inhibits a step at the beginning of the pathway for its biosynthesis.

Phosphofructokinase, the enzyme that converts fructose-6-phosphate to fructose-1,6-bisphosphate, is the next enzyme that catalyzes an irreversible reaction in glycolysis. It, too, is a regulatory enzyme. A high concentration of ATP in the cell is a signal that ATP is being produced faster than it is being consumed, so there is no reason to continue to break down glucose. Therefore, ATP is an inhibitor of phosphofructokinase. It inhibits the enzyme by binding to it and causing a conformational change that decreases its

An allosteric site is a site other than the active site.

affinity for its substrate. ATP is an example of an allosteric inhibitor. An **allosteric inhibitor** inhibits an enzyme by binding to a site on the enzyme other than the active site (*allos* and *stereos* are Greek terms for "other" and "space," respectively). This affects the shape of the active site, which, in turn, affects its ability to catalyze a reaction. On the other hand, high concentrations of ADP and AMP in the cell are a signal that ATP is being consumed faster than it is being produced. Therefore, ADP and AMP are **allosteric activators** of phosphofructokinase. They bind to the enzyme and reverse the inhibition that was brought on by binding ATP.

Citrate is also an allosteric inhibitor of phosphofructokinase. A high concentration of citrate (a citric acid cycle intermediate) in a cell signals that the cell is currently meeting its energy needs by the oxidation of fats and proteins, so the oxidation of carbohydrates can be stopped temporarily.

Pyruvate carboxylase, the first enzyme that catalyzes an irreversible reaction in gluconeogenesis, is also a regulatory enzyme. Pyruvate can be converted to oxaloacetate (by pyruvate carboxylase) and then go on to make glucose for energy storage, or it can be converted to acetyl-CoA (by the pyruvate dehydrogenase complex), which then enters the citric acid cycle to be metabolized for energy. Acetyl-CoA is an allosteric activator of pyruvate carboxylase and a feedback inhibitor of the pyruvate dehydrogenase complex. A high concentration of acetyl-CoA signals that there is currently no need for energy, so pyruvate is converted to glucose rather than prepared to enter the citric acid cycle.

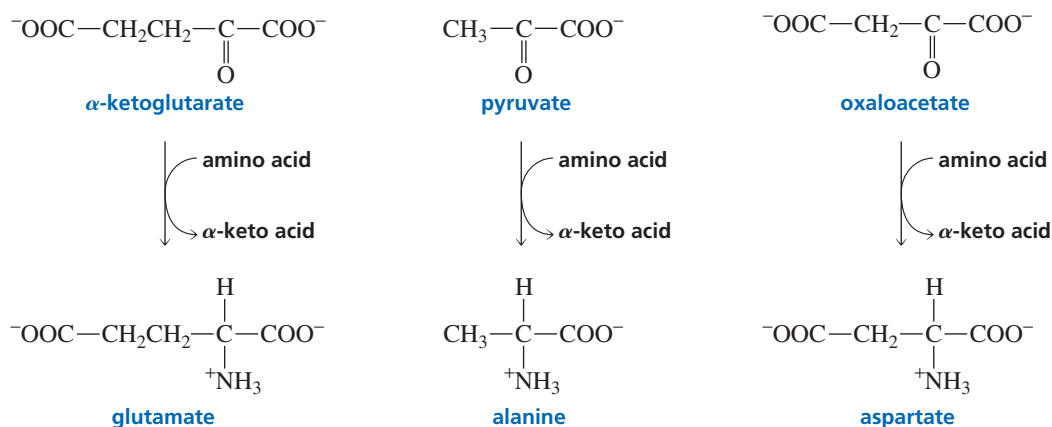
activated by acetyl-CoA
inhibited by acetyl-CoA
pyruvate
pyruvate carboxylase → oxaloacetate
pyruvate dehydrogenase complex → acetyl-CoA

19.13 AMINO ACID BIOSYNTHESIS

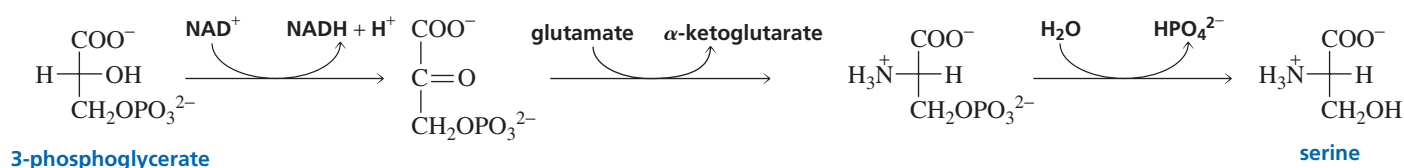
The only amino acids synthesized by the body are the 10 nonessential amino acids—the others must be obtained from food. All the nonessential amino acids are biosynthesized from one of four metabolic intermediates: α-ketoglutarate, pyruvate, oxaloacetate, or 3-phosphoglycerate. Each amino acid has its own pathway for its biosynthesis.

For example, glutamate is biosynthesized by a transamination reaction, using an amino acid as the nitrogen donor and α-ketoglutarate as the nitrogen acceptor. Alanine and aspartate also are biosynthesized by a transamination reaction, using an amino acid as the nitrogen donor and pyruvate and oxaloacetate, respectively, as the nitrogen acceptor.

$^-OOC—CH_2CH_2—C(=O)—COO^-$ **α-ketoglutarate** → (amino acid → α-keto acid) → $^-OOC—CH_2CH_2—CH(^+NH_3)—COO^-$ **glutamate**

$CH_3—C(=O)—COO^-$ **pyruvate** → (amino acid → α-keto acid) → $CH_3—CH(^+NH_3)—COO^-$ **alanine**

$^-OOC—CH_2—C(=O)—COO^-$ **oxaloacetate** → (amino acid → α-keto acid) → $^-OOC—CH_2—CH(^+NH_3)—COO^-$ **aspartate**

Serine is biosynthesized by oxidizing 3-phosphoglycerate (an intermediate in glycolysis), transaminating the product with glutamate and then hydrolyzing off the phosphate group. In Section 21.9, we will see how proteins are biosynthesized from amino acids.

$$\underset{\text{3-phosphoglycerate}}{\text{H}-\overset{\text{COO}^-}{\underset{\text{CH}_2\text{OPO}_3^{2-}}{\text{C}}}-\text{OH}} \xrightarrow[\text{NAD}^+ \rightarrow \text{NADH} + \text{H}^+]{} \overset{\text{COO}^-}{\underset{\text{CH}_2\text{OPO}_3^{2-}}{\text{C}=\text{O}}} \xrightarrow[\text{glutamate} \rightarrow \alpha\text{-ketoglutarate}]{} \text{H}_3\overset{+}{\text{N}}-\overset{\text{COO}^-}{\underset{\text{CH}_2\text{OPO}_3^{2-}}{\text{C}}}-\text{H} \xrightarrow[\text{H}_2\text{O} \rightarrow \text{HPO}_4^{2-}]{} \underset{\text{serine}}{\text{H}_3\overset{+}{\text{N}}-\overset{\text{COO}^-}{\underset{\text{CH}_2\text{OH}}{\text{C}}}-\text{H}}$$

PROBLEM 18

Glutamine is biosynthesized from glutamate in two steps using ATP and ammonia. The other product is ADP. Propose a mechanism for this biosynthesis. (*Hint*: see Section 19.1.)

SOME IMPORTANT THINGS TO REMEMBER

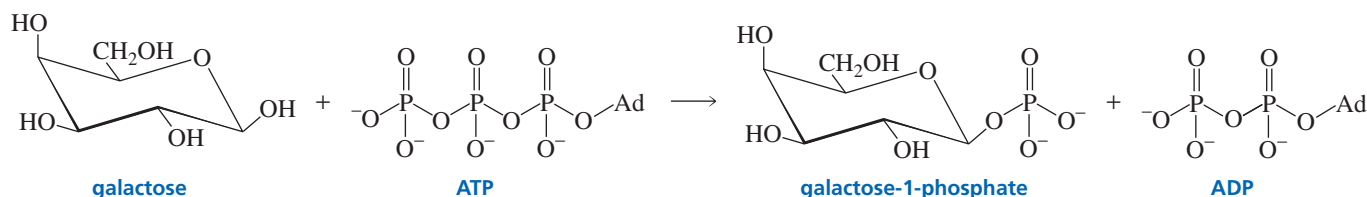
- **Metabolism** is the set of reactions living organisms carry out to obtain energy and to synthesize the compounds they need. Metabolism can be divided into catabolism and anabolism.
- A **catabolic pathway** is a series of reactions that breaks down a complex biomolecule to provide energy and simpler molecules.
- An **anabolic pathway** is a series of reactions that leads to the synthesis of a complex biomolecule from simpler molecules.
- ATP is a cell's most important source of chemical energy; ATP provides a reaction pathway involving a good leaving group for a reaction that would not otherwise occur because of a poor leaving group. This occurs by the way of a phosphoryl transfer reaction.
- A **phosphoryl transfer reaction** involves the transfer of a phosphoryl group of ATP to a nucleophile as a result of breaking a **phosphoanhydride bond.**
- A phosphoryl transfer reaction forms one of three intermediates—an **acyl** (or **alkyl) phosphate,** an **acyl** (or **alkyl) pyrophosphate,** or an **acyl** (or **alkyl) adenylate.**
- The reaction of a nucleophile with a phosphoanhydride bond is highly exergonic because of electrostatic repulsion, solvation, and electron delocalization.
- **Catabolism** can be divided into four stages. In the *first stage*, fats, carbohydrates, and proteins are hydrolyzed to fatty acids, monosaccharides, and amino acids.
- In the *second stage*, the products obtained from the first stage are converted to compounds that can enter the citric acid cycle. In order to enter the citric acid cycle, a compound must be either a citric acid cycle intermediate, acetyl-CoA, or pyruvate (because it can be converted to acetyl-CoA).
- In the *second stage*, a fatty acyl-CoA is converted to acetyl-CoA in a pathway called ***β*-oxidation.** The series of four reactions is repeated until the entire fatty acid has been converted to acetyl-CoA molecules.
- In the *second stage*, glucose is converted to two molecules of pyruvate in a series of 10 reactions known as **glycolysis.**
- Under aerobic conditions, pyruvate is converted to acetyl-CoA, which then enters the citric acid cycle.
- In the second stage, amino acids are metabolized to pyruvate, acetyl-CoA, and/or citric acid cycle intermediates, depending on the amino acid.
- The **citric acid cycle** is *the third stage* of catabolism. It is a series of eight reactions that converts the acetyl group of each molecule of acetyl-CoA that enters the cycle to two molecules of CO_2.
- In *the fourth stage* of catabolism, called **oxidative phosphorylation,** each molecule of NADH and $FADH_2$ formed in oxidation reactions in the second and third stages of catabolism is converted into 2.5 molecules of ATP and 1.5 molecules of ATP, respectively.
- **Anabolism** is the reverse of catabolism. In anabolism, acetyl-CoA, pyruvate, glycolytic intermediates, and citric acid cycle intermediates are the starting materials for the synthesis of fatty acids, carbohydrates, and proteins.
- A **kinase** is an enzyme that puts a phosphate group on its substrate.
- A **phosphatase** is an enzyme that takes a phosphate group off its substrate.
- Many of the reactions involved in the synthesis of glucose from pyruvate—**gluconeogenesis**—are carried out by the same enzymes that catalyze the reactions in glycolysis—they are just operating in reverse.
- Some of the enzymes near the beginning of each pathway catalyze essentially irreversible reactions, and those reactions need an enzyme that catalyzes the reverse reaction when going in the other direction.
- The enzyme that catalyzes an irreversible reaction near the beginning of the pathway is a **regulatory enzyme**—it can be activated and inhibited.

- A **feedback inhibitor** inhibits a step at the beginning of the pathway for its biosynthesis.
- An **allosteric inhibitor** or **activator** inhibits or activates an enzyme by binding to a site on the enzyme other than the active site, which affects the function of the active site.
- All the nonessential amino acids are biosynthesized from one of four metabolic intermediates: pyruvate, oxaloacetate, α-ketoglutarate, or 3-phosphoglycerate.

PROBLEMS

19. Indicate whether an anabolic pathway or a catabolic pathway does the following:
a. produces energy in the form of ATP **b.** involves primarily oxidation reactions

20. Galactose can enter the glycolytic pathway but it must first react with ATP to form galactose-1-phosphate. Propose a mechanism for this reaction.

galactose + ATP ⟶ galactose-1-phosphate + ADP

21. When pyruvate is reduced by NADH to lactate, which hydrogen in lactate comes from NADH?

22. Which of the ten reactions in glycolysis are
a. phsophorylations? **b.** isomerizations? **c.** reductions? **d.** dehydrations?

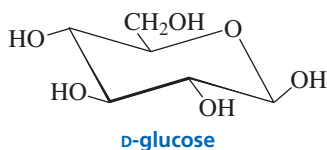
23. Which reactions in the citric acid cycle form a product with a new asymmetric center?

24. Acyl-CoA synthase is the enzyme that activates a fatty acid by converting it to a fatty acyl-CoA (Section 19.4) in a series of two reactions. In the first reaction, the fatty acid reacts with ATP and one of the products formed is ADP. The other product reacts in a second reaction with CoASH to form the fatty acyl-CoA. Propose a mechanism for each of the reactions.

25. In some brain cancers, isocitrate dehydrogenase, instead of catalyzing the oxidation of the secondary alcohol of isocitrate, catalyzes the reduction of α-ketoglutarate. Draw the product of the reaction.

26. If the phosphorus atom in 3-phosphoglycerate is radioactively labeled, where will the label be when the reaction that forms 2-phosphoglycerate is over?

27. Which enzyme is used in gluconeogenesis but not glycolysis?

28. Which carbon atoms of glucose end up as a carboxyl group in pyruvate?

D-glucose

29. Which carbon atoms of glucose end up in ethanol under anaerobic conditions in yeast?

30. How would blood glucose levels be affected before and after a 24-hour fast if there is a deficiency of fructose-1,6-bisphosphatase?

31. Explain why the conversion of pyruvate to lactate is a reversible reaction but the conversion of pyruvate to acetaldehyde is not reversible.

32. How many molecules of NADH are obtained from the conversion of one molecule of glucose 1-phosphate to two molecules of pyruvate by the glycolytic pathway?

33. How many molecules of ATP are obtained from the conversion of one molecule of glucose 1-phosphate to two molecules of pyruvate by the glycolytic pathway?

34. How many molecules of NAD^+ are obtained from the conversion of one molecule of glucose 1-phosphate to two molecules of pyruvate by the glycolytic pathway?

35. What combination of cofactors is involved in the conversion of pyruvate to acetyl-CoA?

36. How many molecules of NADH are obtained in the conversion of one molecule of pyruvate to three molecules of CO_2 via pyruvate dehydrogenase and the citric cycle?

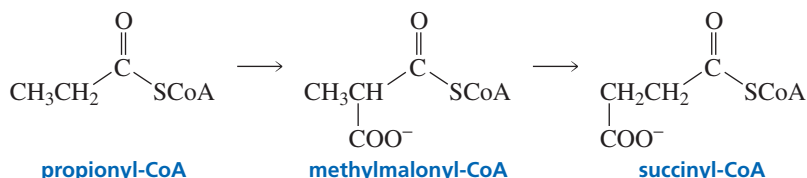
37. How many molecules of $NADH_2$ are obtained in the conversion of one molecule of pyruvate to three molecules of CO_2 via pyruvate dehydrogenase and the citric cycle?

38. How many molecules of ATP are obtained in the conversion of one molecule of pyruvate to three molecules of CO_2 via pyruvate dehydrogenase and the citric cycle?

39. What are the four possible fates of pyruvate in a mammalian cell?

40. Most fatty acids have an even number of carbons and, therefore, are completely metabolized to acetyl-CoA. A fatty acid with an odd number of carbons is metabolized to acetyl-CoA and one equivalent of propionyl-CoA. The following two reactions convert propionyl-CoA into succinyl-CoA, a citric acid cycle intermediate, so that it can be further metabolized. Each of the reactions requires a coenzyme. Identify the coenzyme for each step. From what vitamins are the coenzymes derived? (*Hint:* see Chapter 18.)

$$CH_3CH_2C(=O)SCoA \longrightarrow CH_3CH(COO^-)C(=O)SCoA \longrightarrow {}^-OOCCH_2CH_2C(=O)SCoA$$

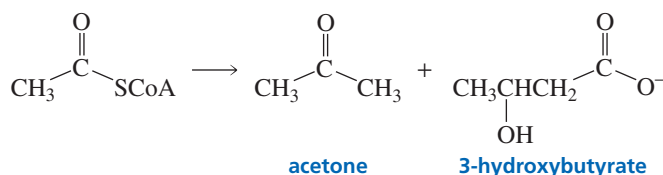
propionyl-CoA methylmalonyl-CoA succinyl-CoA

41. If glucose is labeled with ^{14}C in the indicated position, where will the label be in pyruvate?

a. glucose-1-^{14}C
b. glucose-2-^{14}C
c. glucose-3-^{14}C
d. glucose-4-^{14}C
e. glucose-5-^{14}C
f. glucose-6-^{14}C

42. Write the reactions for the synthesis of citrate from two equivalents of pyruvate. What enzymes are required for the reactions?

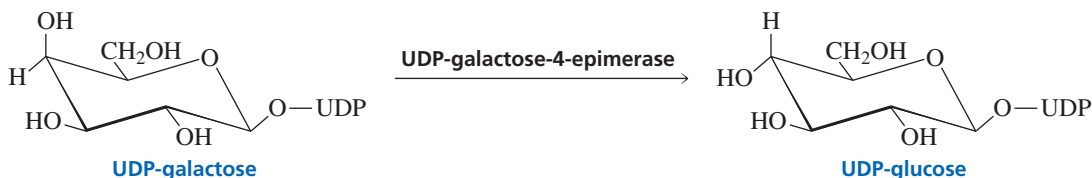
43. Under conditions of starvation, acetyl-CoA, instead of being degraded in the citric acid cycle, is converted to acetone and 3-hydroxybutyrate, which are compounds (called ketone bodies) that the brain can use as a temporary fuel. Propose a mechanism for their formation.

$$CH_3C(=O)SCoA \longrightarrow CH_3C(=O)CH_3 + CH_3CH(OH)CH_2C(=O)O^-$$

acetone 3-hydroxybutyrate

44. Shortly after ^{14}C-labeled glyceraldehyde-3-phosphate is added to a yeast extract, fructose-1,6-bisphosphate labeled at C-3 and C-4 can be isolated. Where was the ^{14}C-label in glyceraldehyde-3-phosphate? How did fructose-1,6-bisphosphate get the second label?

45. UDP-galactose-4-epimerase converts UDP-galactose to UDP-glucose. The reaction requires NAD^+ as a coenzyme.

a. Propose a mechanism for the reaction.
b. Why is the enzyme called an epimerase?

UDP-galactose —UDP-galactose-4-epimerase→ UDP-glucose

46. A student is trying to determine the mechanism for a reaction that uses ATP to activate a carboxylate ion, which then reacts with a thiol. If the carboxylate ion attacks the γ-phosphorus of ATP, the reaction products are the thioester, ADP, and phosphate. However, whether it attacks the α-phosphorus or the β-phosphorus of ATP cannot be determined from the reaction products because the thioester, AMP, and pyrophosphate would be the products in both reactions. The mechanisms can be distinguished by a labeling experiment in which the enzyme, the carboxylate ion, ATP, and radioactively labeled pyrophosphate are incubated, and ATP is isolated. If the isolated ATP is radioactive, attack occurred on the α-phosphorus. If it is not radioactive, then attack occurred on the β-phosphorus. Explain these conclusions.

47. What would be the results of the experiment in Problem 46 if radioactive AMP were added to the incubation mixture instead of radioactive pyrophosphate?

20 The Organic Chemistry of Lipids

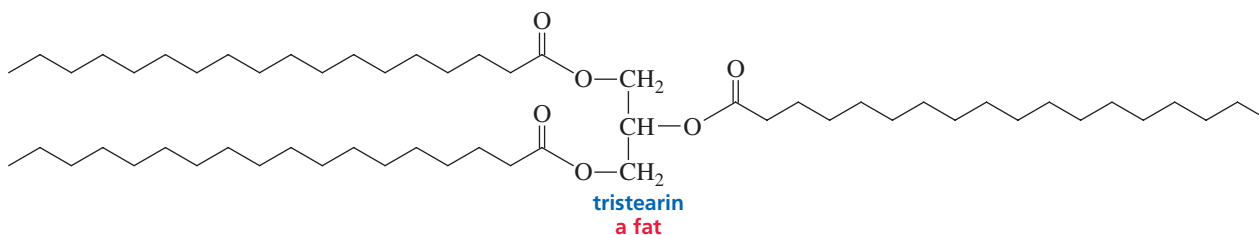
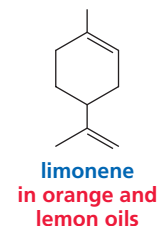
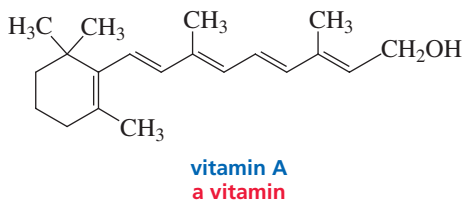
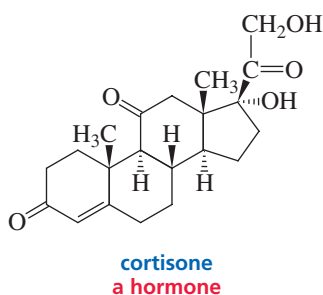
Some of the things you will learn in this chapter are the purpose of the large deposit of fat in a whale's head, the difference between a fat and an oil, and why the venom of some snakes is poisonous.

Lipids are organic compounds, found in living organisms, that are soluble in nonpolar solvents. Because compounds are classified as lipids on the basis of a physical property—their solubility—rather than on the basis of their structure, lipids have a variety of structures and functions, as the following examples illustrate:

cortisone
a hormone

vitamin A
a vitamin

limonene
in orange and lemon oils

tristearin
a fat

The ability of lipids to dissolve in nonpolar solvents results from their significant hydrocarbon component—the part of the molecule responsible for its "oiliness" or "fattiness." The word *lipid* comes from the Greek *lipos*, which means "fat."

20.1 FATTY ACIDS ARE LONG-CHAIN CARBOXYLIC ACIDS

The first lipids we will look at are fatty acids. **Fatty acids** are carboxylic acids with long hydrocarbon chains that are found in nature (Table 20.1). They are unbranched and contain an even number of carbons, because they are synthesized from acetate, a compound with two carbons. The mechanism for their biosynthesis is discussed in Section 13.10.

Table 20.1 Common Naturally Occurring Fatty Acids

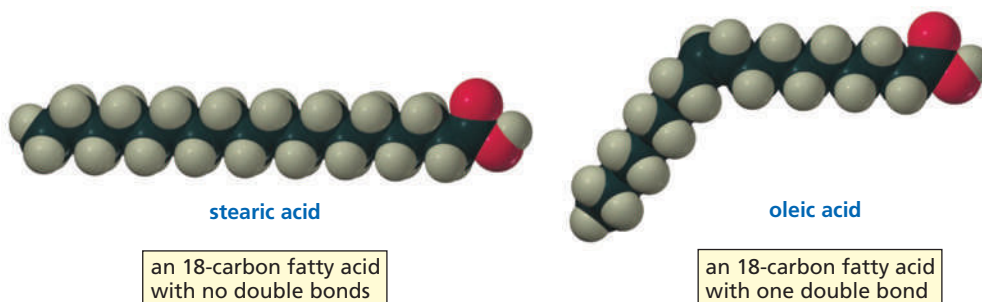
Number of carbons	Common name	Systematic name	Structure	Melting point (°C)
Saturated				
12	lauric acid	dodecanoic acid	COOH	44
14	myristic acid	tetradecanoic acid	COOH	58
16	palmitic acid	hexadecanoic acid	COOH	63
18	stearic acid	octadecanoic acid	COOH	69
20	arachidic acid	eicosanoic acid	COOH	77
Unsaturated				
16	palmitoleic acid	(9*Z*)-hexadecenoic acid	COOH	0
18	oleic acid	(9*Z*)-octadecenoic acid	COOH	13
18	linoleic acid	(9*Z*,12*Z*)-octadecadienoic acid	COOH	–5
18	linolenic acid	(9*Z*,12*Z*,15*Z*)-octadecatrienoic acid	COOH	–11
20	arachidonic acid	(5*Z*,8*Z*,11*Z*,14*Z*)-eicosatetraenoic acid	COOH	–50

Fatty acids can be saturated with hydrogen (and, therefore, have no carbon–carbon double bonds) or unsaturated (and have carbon–carbon double bonds). Fatty acids with more than one double bond are called **polyunsaturated fatty acids.**

The melting points of saturated fatty acids increase with increasing molecular weight because of increased van der Waals interactions between the molecules (Section 3.7). The melting points of unsaturated fatty acids with the same number of double bonds also increase with increasing molecular weight (Table 20.1).

The double bonds in naturally occurring unsaturated fatty acids have the cis configuration, and the double bonds are always separated by one CH_2 group. The cis double bond produces a bend in the molecule, which prevents unsaturated fatty acids from packing together as tightly as saturated fatty acids. As a result, unsaturated fatty acids have fewer

Unsaturated fatty acids have lower melting points than saturated fatty acids.

intermolecular interactions and, therefore, have lower melting points than saturated fatty acids with comparable molecular weights (Table 20.1).

PROBLEM 1

Explain the difference in the melting points of the following fatty acids:

a. palmitic acid and stearic acid
b. palmitic acid and palmitoleic acid
c. oleic acid and linoleic acid

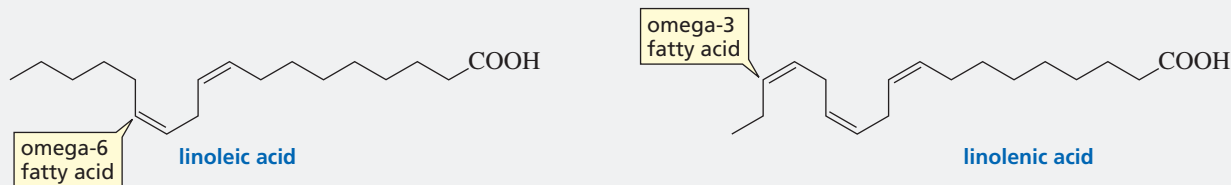
Omega Fatty Acids

Omega indicates the position of the first double bond in an unsaturated fatty acid, counting from the methyl end. For example, linoleic acid is an omega-6 fatty acid because its first double bond is after the sixth carbon, and linolenic acid is an omega-3 fatty acid because its first double bond is after the third carbon. Mammals lack the enzyme that introduces a double bond beyond C-9, counting from the carbonyl carbon. Linoleic acid and linolenic acid are, therefore, *essential fatty acids* for mammals: mammals cannot synthesize them, but since they are needed for normal body function, they must be obtained from the diet.

Omega-3 fatty acids have been found to decrease the likelihood of sudden death due to a heart attack. When under stress, the heart can develop fatal disturbances in its rhythm. Omega-3 fatty acids are incorporated into cell membranes in the heart and apparently have a stabilizing effect on heart rhythm. These fatty acids are found in fatty fish such as herring, mackerel, and salmon.

Linoleic and linolenic acids are essential fatty acids for mammals.

COOH
omega-6 fatty acid
linoleic acid

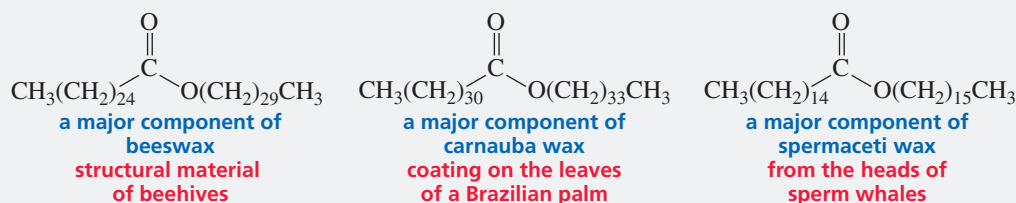
omega-3 fatty acid
COOH
linolenic acid

Waxes Are Esters That Have High Molecular Weights

Waxes are another class of lipid. They are esters that are formed from long-chain carboxylic acids and long-chain alcohols. For example, beeswax, the structural material of beehives, is an ester with a 26-carbon carboxylic acid component and a 30-carbon alcohol component. The word *wax* comes from the Old English *weax*, meaning "material of the honeycomb." Carnauba wax is a very hard wax because of its relatively high molecular weight; it has a 32-carbon carboxylic acid component and a 34-carbon alcohol component. Carnauba wax is widely used as a car wax and in floor polishes.

layers of honeycomb in a beehive

$$CH_3(CH_2)_{24}\overset{O}{\overset{\|}{C}}O(CH_2)_{29}CH_3$$
a major component of beeswax
structural material of beehives

$$CH_3(CH_2)_{30}\overset{O}{\overset{\|}{C}}O(CH_2)_{33}CH_3$$
a major component of carnauba wax
coating on the leaves of a Brazilian palm

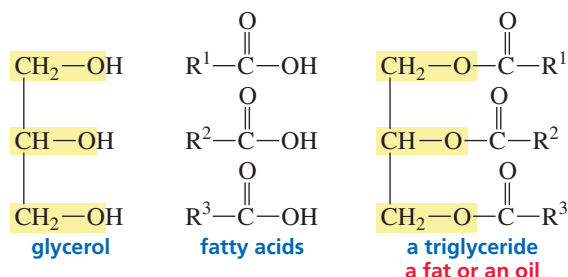
$$CH_3(CH_2)_{14}\overset{O}{\overset{\|}{C}}O(CH_2)_{15}CH_3$$
a major component of spermaceti wax
from the heads of sperm whales

Waxes are common in the biological world. The feathers of birds are coated with wax to make them water repellent. Some vertebrates secrete wax in order to keep their fur lubricated and water repellent. Insects secrete a waterproof, waxy layer on the outside of their exoskeletons. Wax is also found on the surfaces of certain leaves and fruits, where it serves as a protectant against parasites and minimizes the evaporation of water.

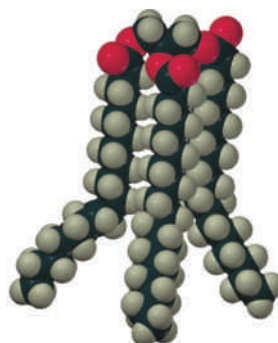
raindrops on a feather

20.2 FATS AND OILS ARE TRIGLYCERIDES

Triglycerides (also called **triacylglycerols**) are lipids in which each of the three OH groups of glycerol has formed an ester with a fatty acid. If the three fatty acid components of a triglyceride are the same, the compound is called a **simple triglyceride. Mixed triglycerides** contain two or three different fatty acid components and are more common than simple triglycerides.

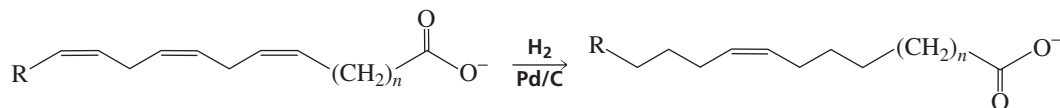
$$\begin{array}{l} CH_2{-}OH \\ | \\ CH{-}OH \\ | \\ CH_2{-}OH \end{array} \qquad \begin{array}{l} R^1{-}\overset{O}{\overset{\|}{C}}{-}OH \\ R^2{-}\overset{O}{\overset{\|}{C}}{-}OH \\ R^3{-}\overset{O}{\overset{\|}{C}}{-}OH \end{array} \qquad \begin{array}{l} CH_2{-}O{-}\overset{O}{\overset{\|}{C}}{-}R^1 \\ | \\ CH{-}O{-}\overset{O}{\overset{\|}{C}}{-}R^2 \\ | \\ CH_2{-}O{-}\overset{O}{\overset{\|}{C}}{-}R^3 \end{array}$$

glycerol — fatty acids — a triglyceride, a fat or an oil

Triglycerides that are solids or semisolids at room temperature are called **fats.** Most fats are obtained from animals and are composed largely of triglycerides with fatty acid components that either are saturated or have only one double bond. The saturated fatty acid tails pack closely together, giving these triglycerides relatively high melting points (Table 20.1). Therefore, they are solids at room temperature.

a fat — an oil

One unsaturated fatty acid—a 20-carbon fatty acid with five double bonds, known as EPA and found in high concentrations in fish oils—is thought to lower the chance of developing certain forms of heart disease. This puffin's diet is high in fish oil.

Liquid triglycerides are called **oils.** Oils typically come from plant products such as corn, soybeans, olives, and peanuts. They are composed primarily of triglycerides with unsaturated fatty acids and, therefore, cannot pack tightly together. Consequently, they have relatively low melting points and so are liquids at room temperature. All triglyceride molecules from a single source are not necessarily identical; most substances, such as lard and olive oil, for example, are mixtures of several different mixed triglycerides.

Some or all of the double bonds of polyunsaturated oils can be reduced by catalytic hydrogenation. Margarine and shortening are prepared by hydrogenating vegetable oils, such as soybean oil or safflower oil, until they have the desired consistency. The hydrogenation reaction must be carefully controlled, however, because reducing all the carbon–carbon double bonds would produce a hard fat with the consistency of beef tallow. We have seen that trans fats can be formed during hydrogenation (Section 5.6).

R–(CH=CH)... $(CH_2)_n$–C(=O)O$^-$ $\xrightarrow[\text{Pd/C}]{H_2}$ R... $(CH_2)_n$–C(=O)O$^-$

Whales and Echolocation

Whales have enormous heads, accounting for 33% of their total weight. They have large deposits of fat in their heads and lower jaws. This fat is very different from both the whale's normal body fat and its dietary fat. Because major anatomical modifications were necessary to accommodate this fat, it must have some important function for the animal.

It is now believed that the fat is used for echolocation—emitting sounds in pulses to gain information by analyzing the returning echoes. The fat in the whale's head focuses the emitted sound waves in a directional beam, and the echoes are received by the fat organ in the lower jaw. This organ transmits the sound to the brain for processing and interpretation, providing the whale with information about the depth of the water, changes in the sea floor, and the location of the coastline. The fat deposits in the whale's head and jaw, therefore, give the animal a unique acoustic sensory system and allow it to compete successfully for survival with the shark, which also has a well-developed sense of sound direction.

PROBLEM 2♦

Which has a higher melting point: glyceryl tripalmitoleate or glyceryl tripalmitate?

PROBLEM 3♦

Draw the structure of an optically inactive fat that, when hydrolyzed, gives glycerol, one equivalent of lauric acid, and two equivalents of stearic acid. *Hint*: see Sections 4.4 and 4.8.

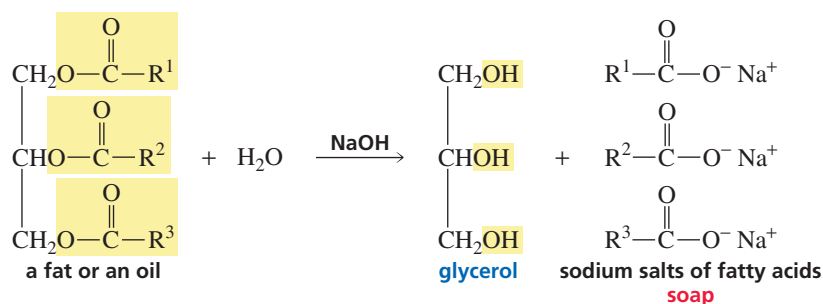
PROBLEM 4♦

Draw the structure of an optically active fat that, when hydrolyzed, gives the same products as the fat in Problem 3.

20.3 SOAPS AND DETERGENTS

When the ester groups of a fat or an oil are hydrolyzed in a basic solution, glycerol and fatty acids are formed. Because the solution is basic, the fatty acids are in their basic forms—namely, RCO_2^-.

$$\begin{array}{l} CH_2O-\overset{O}{\overset{\|}{C}}-R^1 \\ | \\ CHO-\overset{O}{\overset{\|}{C}}-R^2 \\ | \\ CH_2O-\overset{O}{\overset{\|}{C}}-R^3 \end{array} + H_2O \xrightarrow{NaOH} \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + \begin{array}{l} R^1-\overset{O}{\overset{\|}{C}}-O^-\,Na^+ \\ R^2-\overset{O}{\overset{\|}{C}}-O^-\,Na^+ \\ R^3-\overset{O}{\overset{\|}{C}}-O^-\,Na^+ \end{array}$$

a fat or an oil — glycerol — sodium salts of fatty acids (soap)

The sodium or potassium salts of fatty acids are what we know as **soap.** Consequently, the hydrolysis of an ester in a basic solution is called **saponification** (the Latin word for "soap" is *sapo*). After hydrolysis, sodium chloride is added to precipitate the soap, which is dried and pressed into bars. Perfume can be added for scented soaps, dyes can be added for colored soaps, sand can be added for scouring soaps, and air can be blown into the soap to make it float in water. Three of the most common soaps are the following:

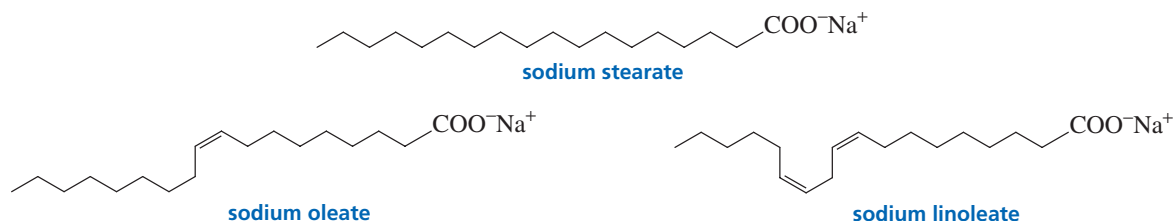
COO^-Na^+

sodium stearate

COO^-Na^+

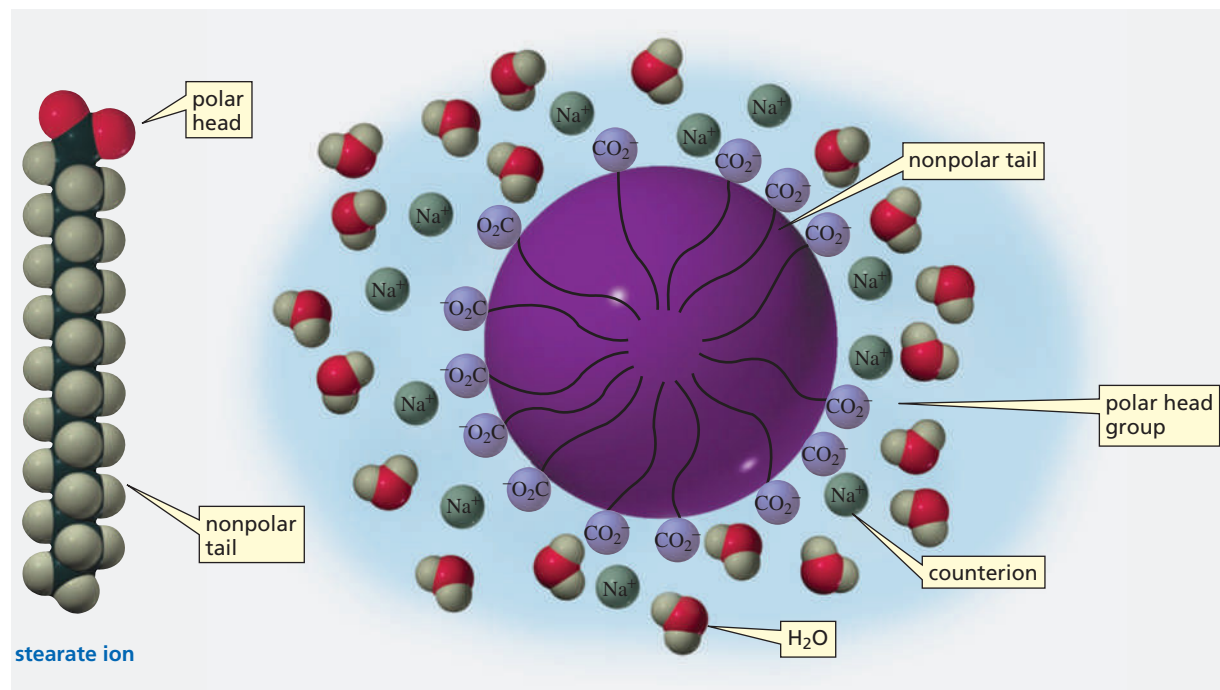
sodium oleate

COO^-Na^+

sodium linoleate

PROBLEM 5 Solved

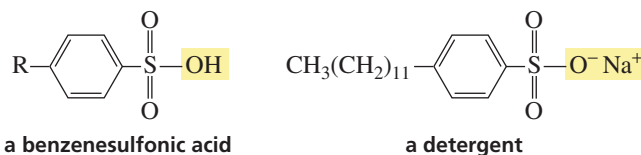
An oil obtained from coconuts is unusual in that all three fatty acid components are identical. The molecular formula of the oil is $C_{45}H_{86}O_6$. What is the molecular formula of the carboxylate ion obtained when the oil is saponified?

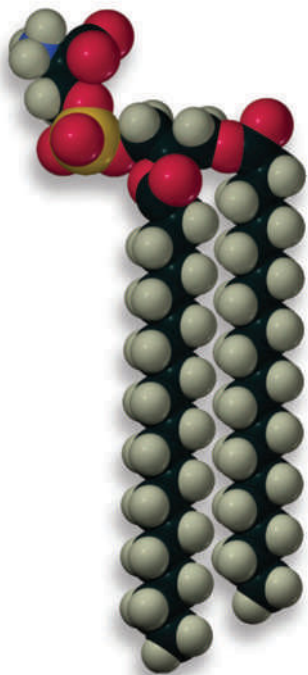
Solution When the oil is saponified, it forms glycerol and three equivalents of carboxylate ion. In losing glycerol, the fat loses three carbons and five hydrogens. Thus, the three equivalents of carboxylate ion have a combined molecular formula of $C_{42}H_{81}O_6$. Dividing by three gives a molecular formula of $C_{14}H_{27}O_2$ for the carboxylate ion.

Long-chain carboxylate ions do not exist as individual ions in aqueous solution. Instead, they arrange themselves in spherical clusters called **micelles.** Each micelle contains 50–100 long-chain carboxylate ions and resembles a large ball. The polar heads of the carboxylate ions, each accompanied by a counterion, are on the outside of the ball because of their attraction for water, whereas the nonpolar tails are buried in the interior of the ball to minimize their contact with water. The hydrophobic interactions between the nonpolar tails increase the stability of the micelle (Section 17.12).

Water by itself is not a very effective cleaner because dirt is carried by nonpolar oil molecules. Soap has cleansing ability because the nonpolar oil molecules dissolve in the nonpolar interior of the micelles and are washed away with the micelle during rinsing.

Because the surface of the micelle is charged, the individual micelles repel each other instead of clustering together to form larger aggregates. However, in "hard" water—water containing high concentrations of calcium and magnesium ions—micelles do form aggregates, which we know as "bathtub ring" or "soap scum."

The formation of soap scum in hard water led to a search for synthetic materials that would have the cleansing properties of soap but would not form scum when they encountered calcium and magnesium ions. The synthetic "soaps" that were developed, known as **detergents** (from the Latin *detergere*, which means "to wipe off"), are salts of benzenesulfonic acids. Calcium and magnesium salts of benzenesulfonic acids do not form aggregates.

a benzenesulfonic acid

a detergent

After the initial introduction of detergents into the marketplace, it was discovered that those with straight-chain alkyl groups are biodegradable, whereas those with branched-chain alkyl groups are not. Therefore, to prevent detergents from polluting rivers and lakes, detergents are made only with straight-chain alkyl groups.

20.4 PHOSPHOGLYCERIDES AND SPHINGOLIPIDS

For organisms to operate properly, some of their parts must be separated from other parts. On a cellular level, for example, the outside of the cell must be separated from the inside. "Greasy" lipid **membranes** serve as the barrier. In addition to isolating the cell's contents, membranes allow the selective transport of ions and organic molecules into and out of the cell.

Phosphoglycerides are the major components of cell membranes. Phosphoglycerides are similar to triglycerides except that a terminal OH group of glycerol is esterified with phosphoric acid rather than with a fatty acid. Therefore, phosphoglycerides belong to the broader class of lipids known as **phospolipids.** The most common phosphoglycerides in membranes have a second phosphate ester linkage—thus, they are phosphodiesters. Phosphoglycerides form **membranes** by arranging themselves in a **lipid bilayer** (see page 125).

The alcohols most commonly used to form the second ester group are ethanolamine, choline, and serine. Phosphatidylethanolamines are also called *cephalins*, and phosphatidylcholines are called *lecithins*. Lecithins are added to foods such as mayonnaise to prevent the aqueous and fat components from separating.

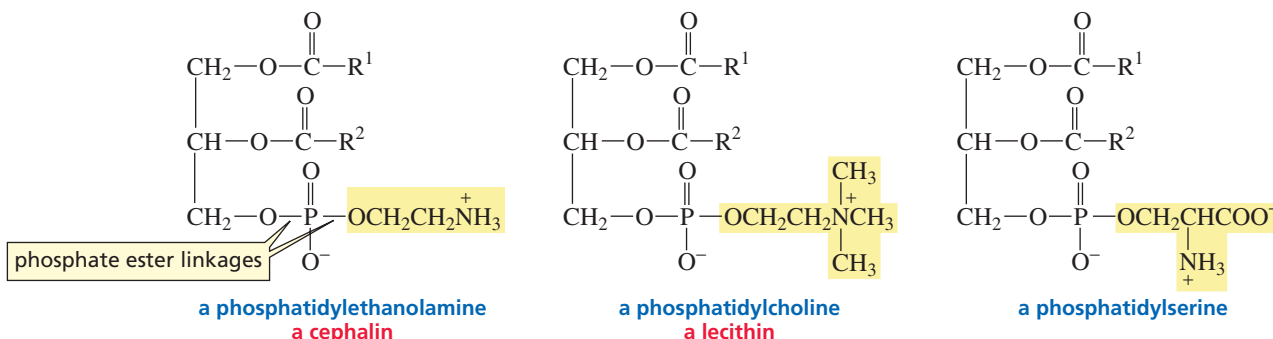
The fluidity of a membrane is controlled by the fatty acid components of the phosphoglycerides. Saturated fatty acids decrease membrane fluidity because their hydrocarbon chains pack closely together. Unsaturated fatty acids increase fluidity because they pack less closely together. Cholesterol also decreases fluidity (see page 125). Only animal membranes contain cholesterol, so they are more rigid than plant membranes.

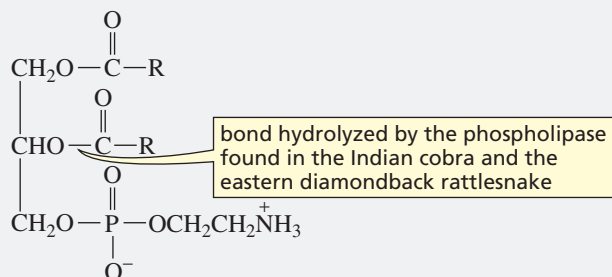
a phosphatidylserine
a phosphoglyceride

phosphoglycerides

a phosphatidylethanolamine
a cephalin

a phosphatidylcholine
a lecithin

a phosphatidylserine

Snake Venom

The venom of some poisonous snakes contains a phospholipase, an enzyme that hydrolyzes an ester group of a phosphoglyceride. For example, both the eastern diamondback rattlesnake and the Indian cobra contain a phospholipase that hydrolyzes an ester bond of cephalins, which causes the membranes of red blood cells to rupture.

an eastern diamondback rattlesnake

PROBLEM 6♦

Membranes contain proteins. Integral membrane proteins extend partly or completely through the membrane, whereas peripheral membrane proteins are found on the inner or outer surface of the membrane. What is the likely difference in the amino acid composition of integral and peripheral membrane proteins?

Lipids that contain a phosphate group are called phospholipids.

PROBLEM 7♦

A colony of bacteria accustomed to an environment with a temperature of 25 °C was moved to an identical environment whose temperature was 35 °C. The higher temperature increased the fluidity of the bacterial membranes. How can the bacteria regain their original membrane fluidity?

PROBLEM 8

The membrane phospholipids in deer have a higher degree of unsaturation in cells closer to the hoof than in cells closer to the body. Why is this trait important for survival?

Sphingolipids are another kind of lipid found in membranes. They are the major lipid components in the myelin sheaths of nerve fibers. Sphingolipids contain an amino alcohol called sphingosine instead of glycerol. In sphingolipids, the amino group of sphingosine is bonded to the acyl group of a fatty acid.

Two of the most common kinds of sphingolipids are *sphingomyelins* and *cerebrosides*. In sphingomyelins, the primary OH group of sphingosine is bonded to phosphocholine or phosphoethanolamine, in a manner similar to the bonding in lecithins and cephalins. In cerebrosides, the primary OH group of sphingosine is bonded to a sugar residue through a β-glycosidic linkage (Section 16.8).

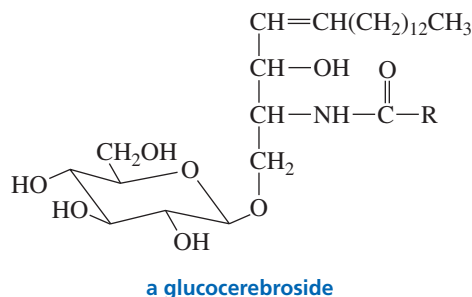
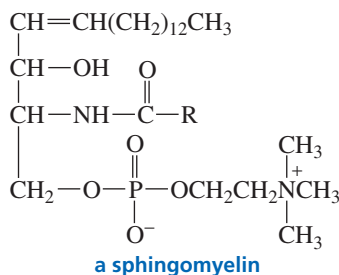
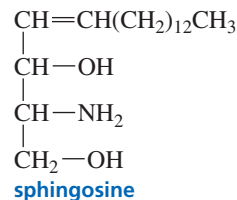
$$\begin{array}{l} CH{=}CH(CH_2)_{12}CH_3 \\ | \\ CH{-}OH \\ | \\ CH{-}NH_2 \\ | \\ CH_2{-}OH \end{array}$$

sphingosine

$$\begin{array}{l} CH{=}CH(CH_2)_{12}CH_3 \\ | \\ CH{-}OH \\ | \\ CH{-}NH{-}\overset{\overset{O}{\|}}{C}{-}R \\ | \\ CH_2{-}O{-}\underset{\underset{O^-}{|}}{\overset{\overset{O}{\|}}{P}}{-}OCH_2CH_2\overset{+}{N}(CH_3)_3 \end{array}$$

a sphingomyelin

$$\begin{array}{l} CH{=}CH(CH_2)_{12}CH_3 \\ | \\ CH{-}OH \\ | \\ CH{-}NH{-}\overset{\overset{O}{\|}}{C}{-}R \\ | \\ CH_2 \\ | \\ O{-}\text{glucose (}\beta\text{; ring with } CH_2OH\text{, HO, HO, OH)} \end{array}$$

a glucocerebroside

Multiple Sclerosis and the Myelin Sheath

The myelin sheath is a lipid-rich covering that is wrapped around the axons of nerve cells. Composed largely of sphingomyelins and cerebrosides, the sheath increases the velocity of nerve impulses. Multiple sclerosis is a disease characterized by loss of the myelin sheath, a consequent slowing of nerve impulses, and eventual paralysis.

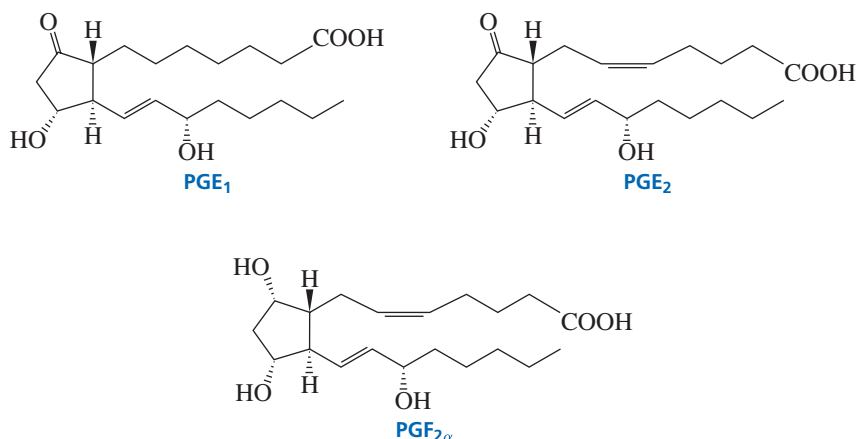
PROBLEM 9

a. Draw the structures of two different sphingomyelins.
b. Draw the structure of a galactocerebroside.

20.5 PROSTAGLANDINS REGULATE PHYSIOLOGICAL RESPONSES

Prostaglandins are found in all body tissues and are responsible for regulating a variety of physiological responses, such as inflammation, blood pressure, blood clotting, fever, pain, the induction of labor, and the sleep–wake cycle. All prostaglandins have a five-membered ring with a seven-carbon carboxylic acid substituent and an adjacent eight-carbon hydrocarbon substituent. The two substituents are trans to each other. How prostaglandins control inflammation and fever is discussed on page 439.

PGE_1 PGE_2

$PGF_{2\alpha}$

Prostaglandins are synthesized from arachidonic acid, a 20-carbon omega-6 fatty acid with four cis double bonds (see page 439). In the cell, arachidonic acid is found esterified to the 2-position of glycerol in many phospholipids. Arachidonic acid is synthesized from linoleic acid, a fatty acid that must be acquired through the diet (Section 20.1).

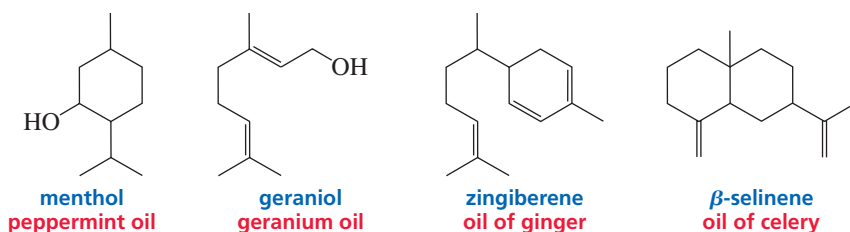
20.6 TERPENES CONTAIN CARBON ATOMS IN MULTIPLES OF FIVE

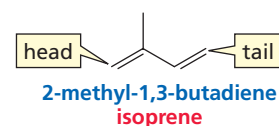
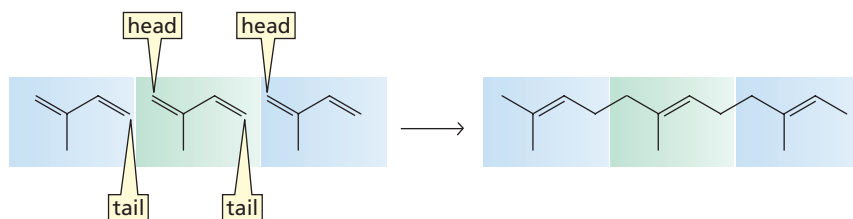
Terpenes are a diverse class of compounds that contain 10, 15, 20, 25, 30, or 40 carbons. More than 20,000 terpenes are known. Many are found in oils extracted from fragrant plants. Terpenes can be hydrocarbons, or they can contain oxygen and be alcohols, ketones, or aldehydes. Oxygen-containing terpenes are sometimes called **terpenoids.** Terpenes and terpenoids have been used as spices, perfumes, and medicines for thousands of years.

menthol
peppermint oil

geraniol
geranium oil

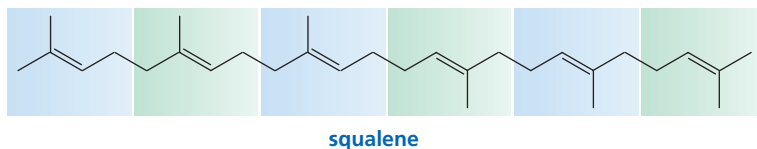
zingiberene
oil of ginger

β-selinene
oil of celery

Terpenes are made by joining together five-carbon isoprene units, usually in a head-to-tail fashion. (The branched end of isoprene is called the head, and the unbranched end is called the tail.) Isoprene is the common name for 2-methyl-1,3-butadiene, a compound with five carbons.

2-methyl-1,3-butadiene
isoprene

In Section 20.7, we will see that the compound actually used in the biosynthesis of terpenes is not isoprene but isopentenyl pyrophosphate, a compound with the same carbon skeleton as isoprene, but with a leaving group that isoprene does not have. We will also look at the mechanism by which isopentenyl pyrophosphate units are joined in a head-to-tail fashion.

Terpenes are classified according to the number of carbons they contain. **Monoterpenes** are composed of two isoprene units, so they have 10 carbons. **Diterpenes** (20 carbons) are composed of four isoprene units. **Sesquiterpenes,** with 15 carbons, have three isoprene units (*sesqui* is from the Latin for "one and a half"). Many fragrances and flavorings found in plants are monoterpenes or sesquiterpenes. These compounds are known as *essential oils*.

A monoterpene has 10 carbons.

Triterpenes (30 carbons) and **tetraterpenes** (40 carbons) have important biological roles. For example, **squalene,** a triterpene, is the precursor of cholesterol, which is the precursor of all the other steroid hormones (Section 3.14). Lycopene and carotene, compounds responsible for the red and orange colors of many fruits and vegetables, are tetraterpenes (see page 389).

squalene

PROBLEM 10♦

One of the linkages in squalene is tail-to-tail, not head-to-tail. What does this suggest about how squalene is synthesized in nature? (*Hint*: Locate the position of the tail-to-tail linkage.)

PROBLEM 11

Mark off the isoprene units in lycopene and β-carotene. (Their structures are on page 389.) Can you detect a similarity in the way in which squalene, lycopene, and β-carotene are biosynthesized?

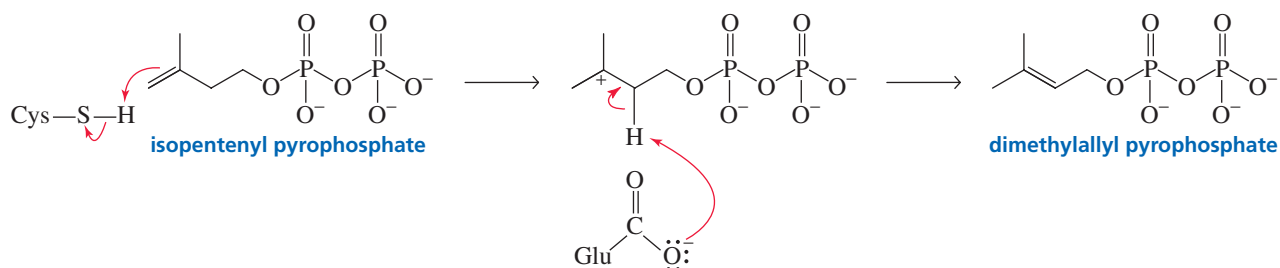
PROBLEM 12

Show the two ways that isoprene linkages can be linked head-to-tail to form menthol. (Menthol's structure is shown on page 643.)

20.7 HOW TERPENES ARE BIOSYNTHESIZED

Both **isopentenyl pyrophosphate** and **dimethylallyl pyrophosphate** are needed for the biosynthesis of terpenes. Therefore, some isopentenyl pyrophosphate must be converted to dimethylallyl pyrophosphate before biosynthesis can take place. This enzyme-catalyzed reaction takes place in two steps.

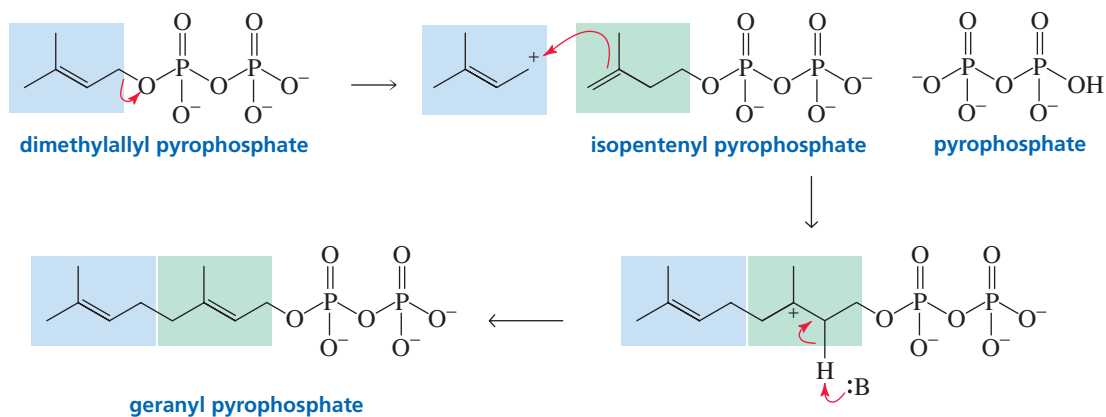
MECHANISM FOR THE CONVERSION OF ISOPENTYL PYROPHOSPHATE TO DIMETHYLALLYL PYROPHOSPHATE

Cys—S—H
isopentenyl pyrophosphate
Glu
dimethylallyl pyrophosphate

Adding a proton and then removing a proton converts isopentenyl pyrophosphate to dimethylallyl pyrophosphate.

- A cysteine side chain is in the proper position at the enzyme's active site to donate a proton to the sp^2 carbon of the alkene that is bonded to the most hydrogens (Section 6.4).
- A glutamate side chain removes a proton from a β-carbon. Recall that the more stable compound is obtained by removing a proton from the β-carbon that is bonded to the fewest hydrogens (Section 8.8).

The enzyme-catalyzed reaction of dimethylallyl pyrophosphate with isopentenyl pyrophosphate forms geranyl pyrophosphate, a 10-carbon compound.

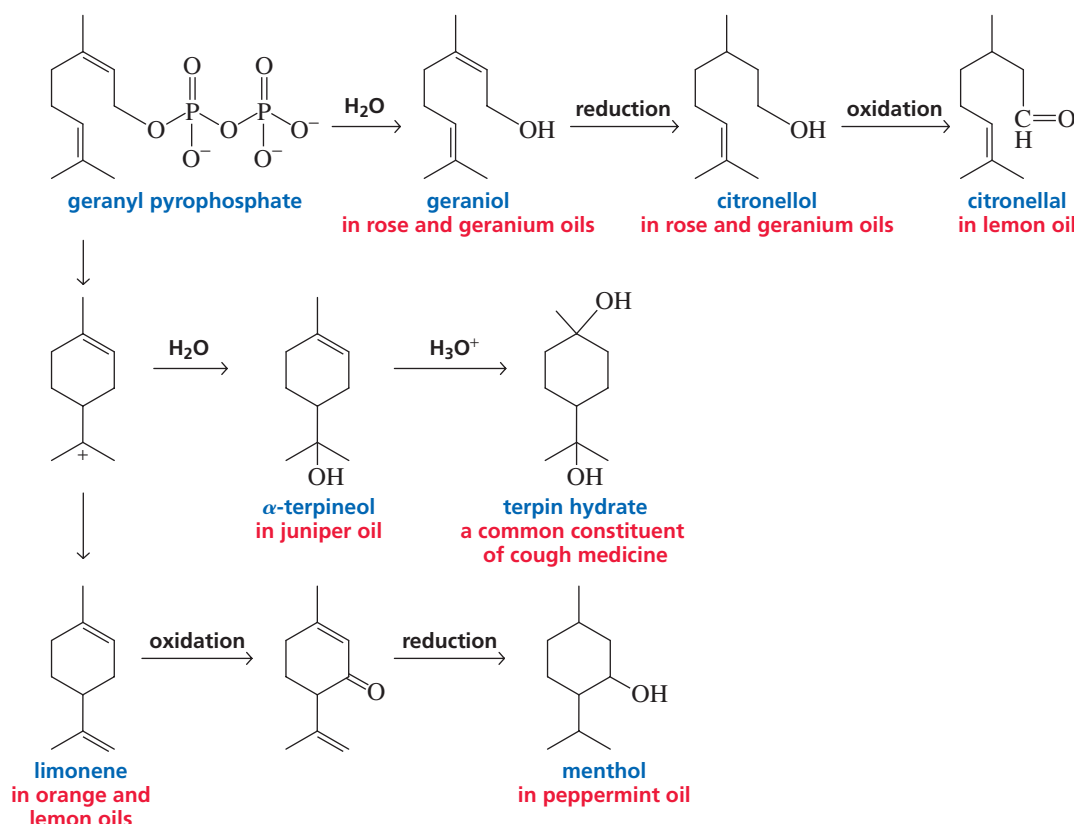
MECHANISM FOR THE BIOSYNTHESIS OF TERPENES

dimethylallyl pyrophosphate
isopentenyl pyrophosphate
pyrophosphate
geranyl pyrophosphate
:B

- Experimental evidence suggests that this is an S_N1 reaction (see Problem 14). Thus, the leaving group of dimethylallyl pyrophosphate departs, forming an allylic cation.
- Isopentenyl pyrophosphate is the nucleophile that adds to the allylic cation.
- A base removes a proton, forming geranyl pyrophosphate.

The scheme shown here shows how some of the many monoterpenes can be synthesized from geranyl pyrophosphate:

geranyl pyrophosphate → (H_2O) geraniol, in rose and geranium oils → (reduction) citronellol, in rose and geranium oils → (oxidation) citronellal, in lemon oil

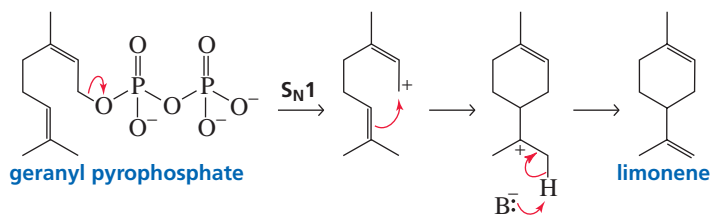
geranyl pyrophosphate → carbocation → (H_2O) α-terpineol, in juniper oil → (H_3O^+) terpin hydrate, a common constituent of cough medicine

carbocation → limonene, in orange and lemon oils → (oxidation) → (reduction) menthol, in peppermint oil

PROBLEM-SOLVING STRATEGY

Proposing a Mechanism for Biosynthesis

Propose a mechanism for the biosynthesis of limonene from geranyl pyrophosphate.

Assuming that geranyl pyrophosphate reacts like dimethylallyl pyrophosphate, the pyrophosphate leaving group departs in an S_N1 reaction. The electrons of the π bond add to the allylic cation, forming the six-membered ring and a new carbocation. A base removes a proton to form the double bond.

geranyl pyrophosphate → (S_N1) → → limonene

Now use the strategy you have just learned to solve Problem 13.

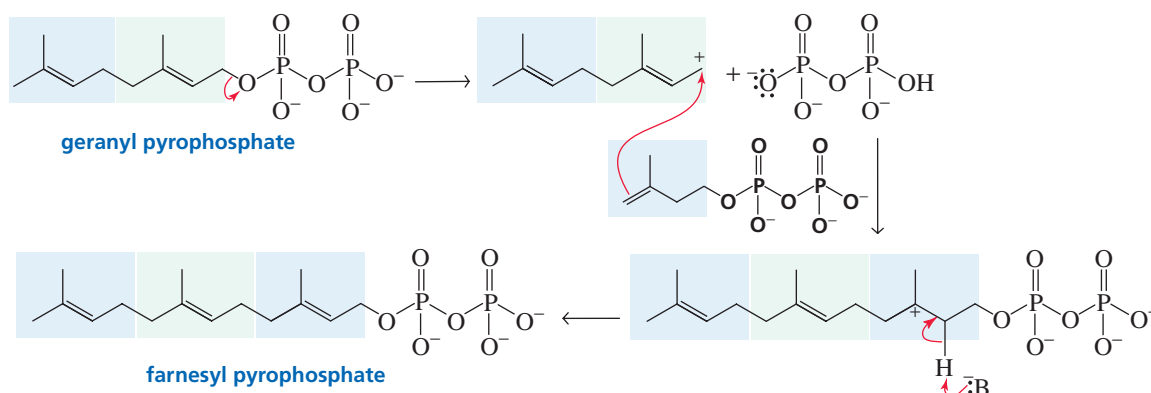
PROBLEM 13

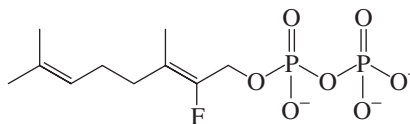
Propose a mechanism for the biosynthesis of α-terpineol from geranyl pyrophosphate.

Geranyl pyrophosphate can react with another molecule of isopentenyl pyrophosphate to form farnesyl pyrophosphate, a 15-carbon compound. Farnesyl pyrophosphate can react with another molecule of isopentenyl pyrophosphate to form geranylgeranyl pyrophosphate, a 20-carbon compound.

dimethylallyl = 5 carbons
isopentenyl = 5 carbons
geranyl = 10 carbons
farnesyl = 15 carbons
geranylgeranyl = 20 carbons

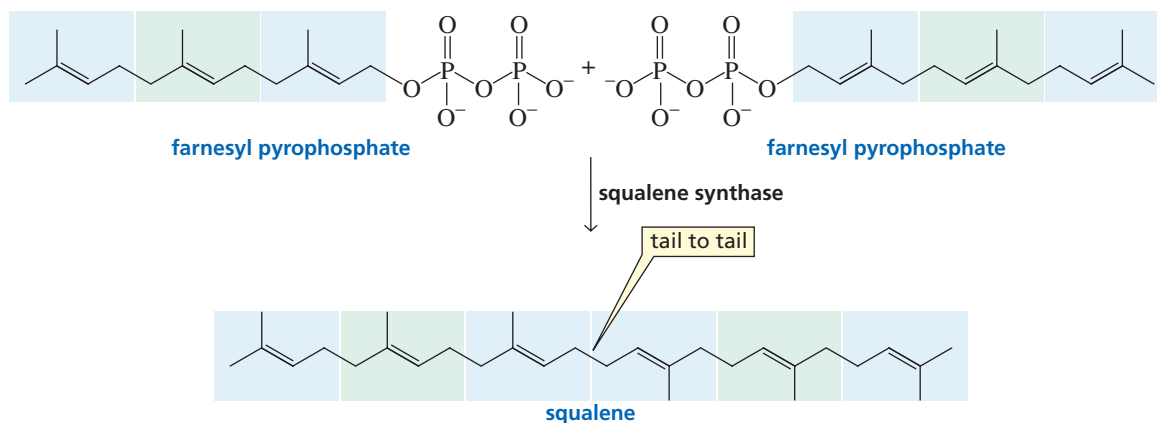
geranyl pyrophosphate

farnesyl pyrophosphate

PROBLEM 14♦

The fluoro-substituted geranyl pyrophosphate shown here reacts with isopentenyl pyrophosphate to form fluoro-substituted farnesyl pyrophosphate. The rate of the reaction is less than 1% of the rate of the reaction when unsubstituted geranyl pyrophosphate is used. What does this tell you about the mechanism of the reaction?

Two molecules of farnesyl pyrophosphate form squalene, a 30-carbon compound. The reaction is catalyzed by the enzyme squalene synthase, which joins the two molecules in a tail-to-tail linkage. As we noted earlier, squalene is the precursor of cholesterol, and cholesterol is the precursor of all the steroid hormones.

farnesyl pyrophosphate + farnesyl pyrophosphate

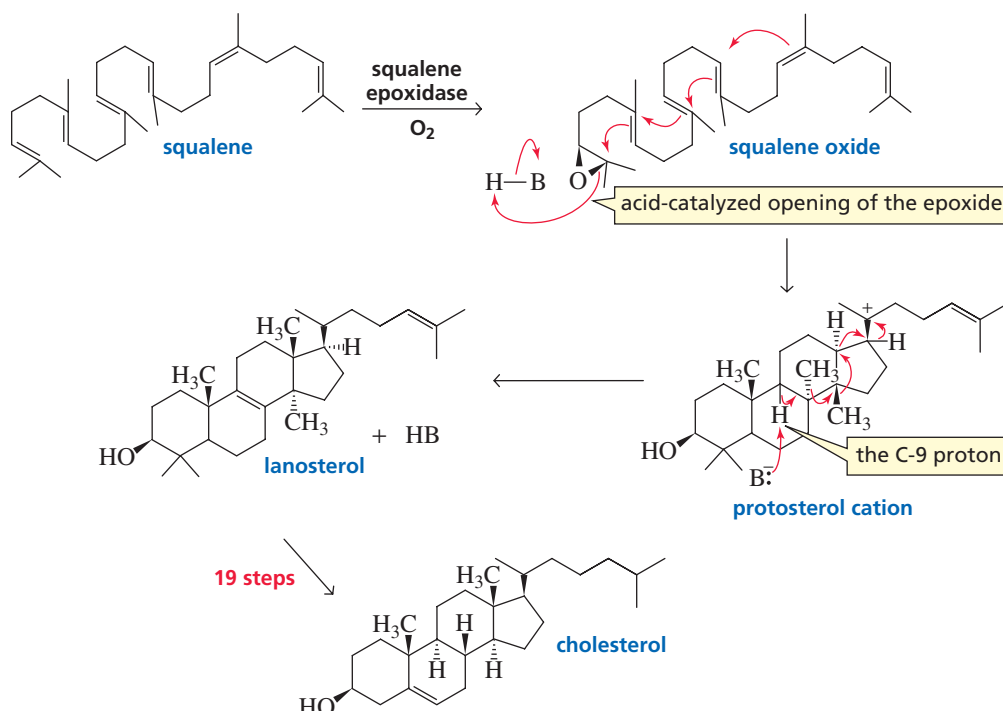
squalene synthase

tail to tail

squalene

20.8 HOW NATURE SYNTHESIZES CHOLESTEROL

We have seen that cholesterol is the precursor of all the steroid hormones (Sections 3.14, 6.10, and 12.0). The starting material for the biosynthesis of cholesterol is the triterpene squalene. Squalene is first converted to lanosterol, which is converted to cholesterol in a series of 19 steps.

STEPS IN THE BIOSYNTHESIS OF LANOSTEROL AND CHOLESTEROL

squalene
squalene epoxidase
O_2
squalene oxide
H—B O
acid-catalyzed opening of the epoxide
protosterol cation
the C-9 proton
H_3C CH_3 H HO B:
lanosterol + HB
19 steps
cholesterol

- The first step is epoxidation of the 2,3-double bond of squalene.
- Acid-catalyzed opening of the epoxide initiates a series of cyclizations resulting in the formation of the protosterol cation.
- Elimination of a C-9 proton from the cation initiates a series of 1,2-hydride and 1,2-methyl shifts, resulting in lanosterol.

Converting lanosterol to cholesterol requires removing three methyl groups from lanosterol, reducing two double bonds, and creating a new double bond. Removing methyl groups from carbon atoms is not easy, and many different enzymes are required to carry out the 19 steps. So why does nature bother? Why not just use lanosterol instead of cholesterol? Konrad Bloch (a Professor of Biochemistry at Harvard University from 1954 to 1982) answered that question when he found that membranes containing lanosterol instead of cholesterol are much more permeable. Small molecules are able to pass easily through lanosterol-containing membranes. As each methyl group is removed from lanosterol, the membrane becomes less and less permeable.

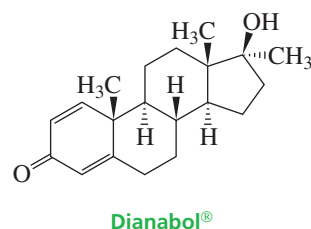
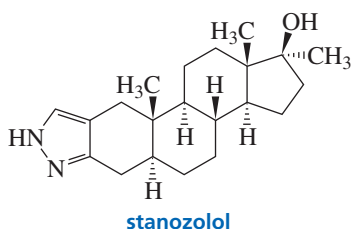
PROBLEM 15♦

Draw the individual 1,2-hydride and 1,2-methyl shifts responsible for conversion of the protosterol cation to lanosterol. How many hydride shifts are involved? How many methyl shifts?

20.9 SYNTHETIC STEROIDS

The potent physiological effects of steroids led scientists, in their search for new drugs, to synthesize steroids that are not available in nature and to investigate their physiological effects. Two such drugs, stanozolol and Dianabol, have the same muscle-building effect as testosterone. Steroids that aid in the development of muscle are called *anabolic steroids*. These drugs are available by prescription and are used to treat people suffering from traumas accompanied by muscle deterioration. The same drugs have been illegally administered to athletes and racehorses to increase their muscle mass. Anabolic steroids,

when taken in relatively high dosages, have been found to cause liver tumors, personality disorders, and testicular atrophy.

stanozolol

Dianabol®

PROBLEM 16

How do testosterone, a natural muscle-building steroid, and Dianabol a synthetic muscle-building steroid, differ in structure? (The structure of testosterone is shown on page 460.)

SOME IMPORTANT THINGS TO REMEMBER

- **Lipids** are organic compounds, found in living organisms, that are soluble in nonpolar solvents.
- **Fatty acids** are carboxylic acids with long, unbranched hydrocarbon chains.
- The cis double bonds in naturally occurring unsaturated fatty acids are separated by one CH_2 group.
- **Waxes** are esters formed from long-chain carboxylic acids and long-chain alcohols.
- **Triglycerides** are compounds in which the three OH groups of glycerol are esterified with fatty acids.
- **Triglycerides** that are solids or semisolids at room temperature are **fats;** liquid triglycerides are **oils.**
- **Phospholipids** are lipids that contain a phosphate group.
- **Phosphoglycerides** differ from triglycerides in that a terminal OH group of glycerol is esterified with phosphoric acid instead of a fatty acid.
- **Sphingolipids** are like phosphoglycerides except they contain sphingosine instead of glycerol.
- **Prostaglandins,** responsible for regulating a variety of physiological responses, are synthesized from arachidonic acid, a 20-carbon fatty acid.
- **Terpenes** are made by joining five-carbon units, usually in a head-to-tail fashion.
- **Monoterpenes**—terpenes with two isoprene units—have 10 carbons, **sesquiterpenes** have 15, **diterpenes** have 20, **triterpenes** have 30, and **tetraterpenes** have 40.
- Isopentenyl pyrophosphate is the five-carbon compound used for the biosynthesis of terpenes.
- The reaction of **dimethylallyl pyrophosphate** (formed from isopentenyl pyrophosphate) with **isopentenyl pyrophosphate** forms geranyl pyrophosphate, a 10-carbon compound.
- Geranyl pyrophosphate can react with another molecule of isopentenyl pyrophosphate to form farnesyl pyrophosphate, a 15-carbon compound.
- Farnesyl pyrophosphate can react with another molecule of isopentenyl pyrophosphate to form geranylgeranyl pyrophosphate, a 20-carbon compound.
- Two molecules of farnesyl pyrophosphate form **squalene,** a 30-carbon compound.
- Squalene is the precursor of **lanosterol,** which is the precursor of cholesterol.
- **Cholesterol** is the precursor of all the steroid hormones.

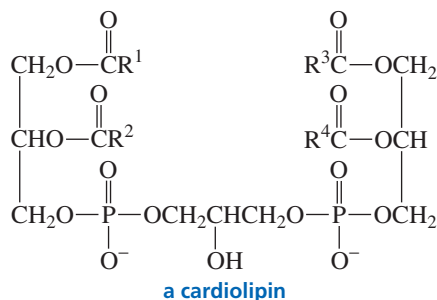
PROBLEMS

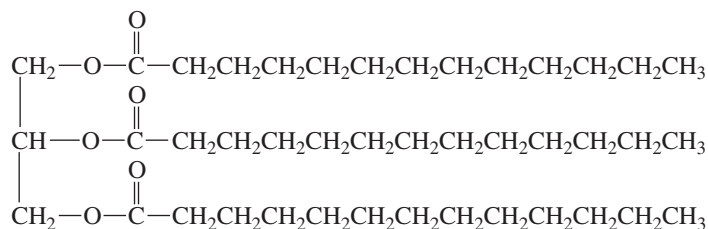
17. Draw the product that would be obtained from the reaction of lanosterol with each of the following reagents:
a. H_2, Pd/C **b.** acetyl chloride **c.** H_2SO_4, Δ **d.** H_2O, H^+ **e.** a peroxyacid

18. Do all triglycerides have the same number of asymmetric centers?

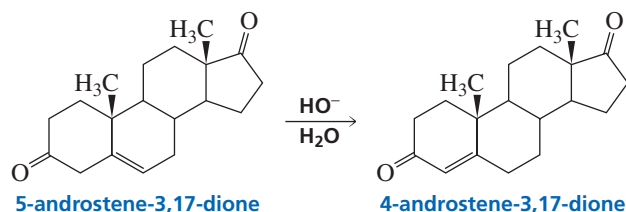
19. Cardiolipins are found in heart muscles. Draw the products formed when a cardiolipin undergoes complete acid-catalyzed hydrolysis.

$$\begin{array}{l} CH_2O{-}\overset{O}{\overset{\|}{C}}R^1 \qquad\qquad R^3\overset{O}{\overset{\|}{C}}{-}OCH_2 \\ CHO{-}\overset{O}{\overset{\|}{C}}R^2 \qquad\qquad R^4\overset{O}{\overset{\|}{C}}{-}OCH \\ CH_2O{-}\underset{O^-}{\underset{|}{\overset{O}{\overset{\|}{P}}}}{-}OCH_2\underset{OH}{\underset{|}{C}}HCH_2O{-}\underset{O^-}{\underset{|}{\overset{O}{\overset{\|}{P}}}}{-}OCH_2 \end{array}$$

a cardiolipin

20. Draw the structure of a simple, fully saturated triglyceride with a molecular weight of 680.

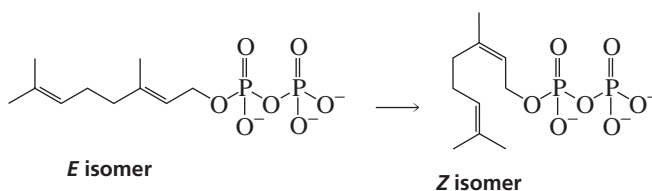
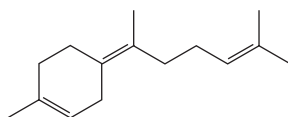
$$\begin{array}{l} CH_2{-}O{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3 \\ CH{-}O{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3 \\ CH_2{-}O{-}\overset{O}{\overset{\|}{C}}{-}CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3 \end{array}$$

21. 5-Androstene-3,17-dione is isomerized to 4-androstene-3,17-dione by hydroxide ion. Propose a mechanism for this reaction.

H_3C H_3C O $\xrightarrow[H_2O]{HO^-}$ H_3C H_3C O

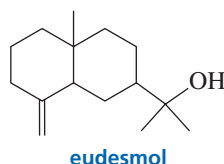
5-androstene-3,17-dione **4-androstene-3,17-dione**

22. **a.** How many different triglycerides are there in which one of the fatty acid components is lauric acid and two are myristic acid?

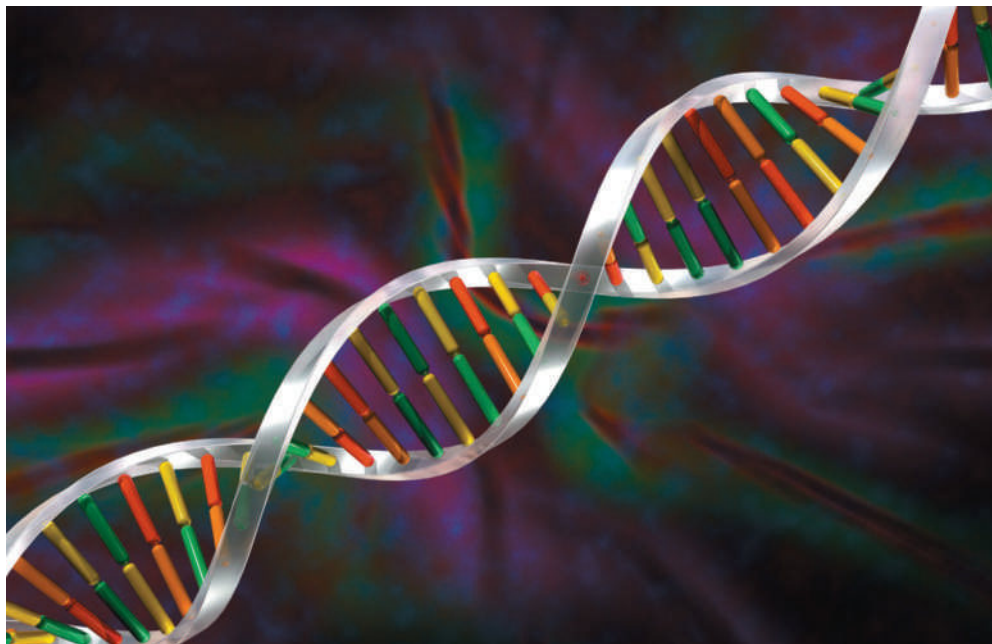
b. How many different triglycerides are there in which one of the fatty acid components is lauric acid, one is myristic acid, and one is palmitic acid?

23. Propose a mechanism for the conversion of the *E* isomer of geranyl pyrophosphate to the *Z* isomer.

***E* isomer** $\longrightarrow$ ***Z* isomer**

24. Farnesyl pyrophosphate forms the sesquiterpene shown here. Propose a mechanism for this reaction.

25. Eudesmol is a sesquiterpene found in eucalyptus. Propose a mechanism for its biosynthesis from farnesyl pyrophosphate.

OH

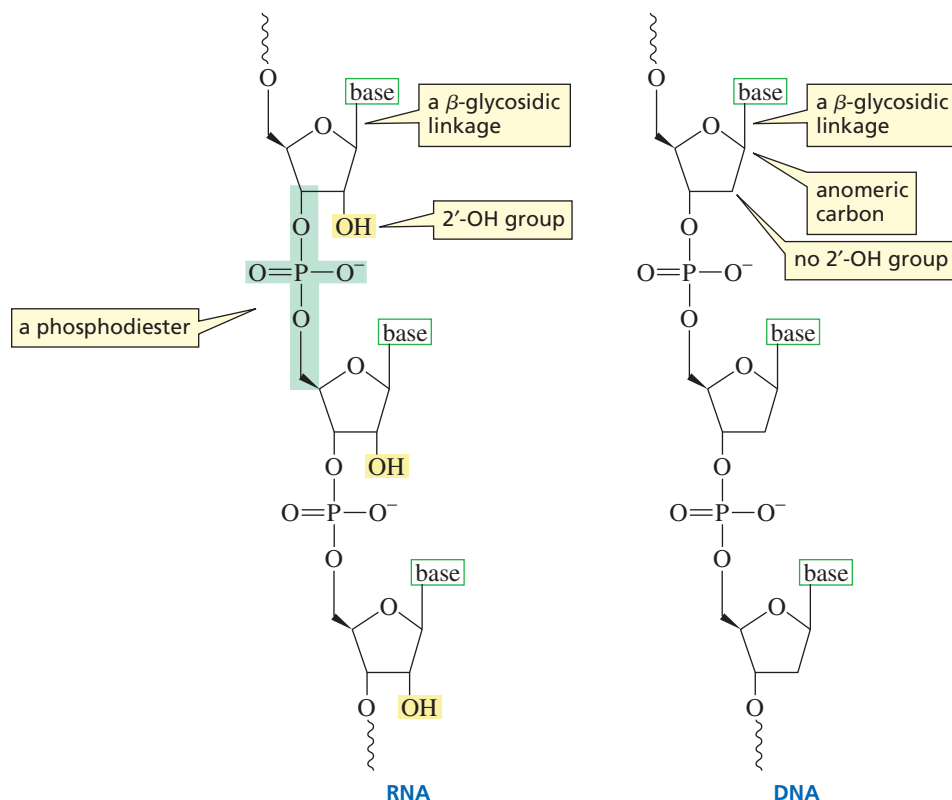
eudesmol

21 The Chemistry of the Nucleic Acids

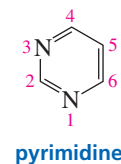
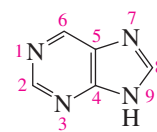
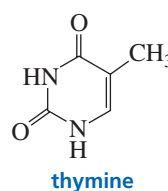
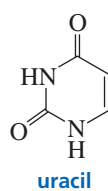
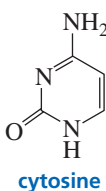
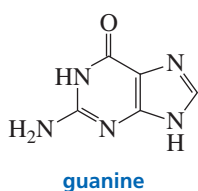
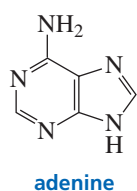
a double helix

We have studied two of the three major kinds of biopolymers: polysaccharides in Chapter 16 and proteins in Chapter 17. Now in this chapter, we will look at the third kind of biopolymer—nucleic acids. There are two types of nucleic acids: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA encodes an organism's entire hereditary information and controls the growth and division of cells. In all organisms (except certain viruses), the genetic information stored in DNA is transcribed into RNA. This information can then be translated for the synthesis of all the proteins needed for cellular structure and function.

DNA was first isolated in 1869 from the nuclei of white blood cells. Because it was found in the nucleus and was acidic, it was called *nucleic acid*. Eventually, scientists found that the nuclei of all cells contain DNA, but not until it was shown in 1944 that DNA could be transferred from one species to another, along with inheritable traits, did they realize that DNA is the carrier of genetic information. In 1953, James Watson and Francis Crick described the three-dimensional structure of DNA—the famed double helix.

21.1 NUCLEOSIDES AND NUCLEOTIDES

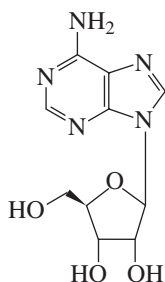
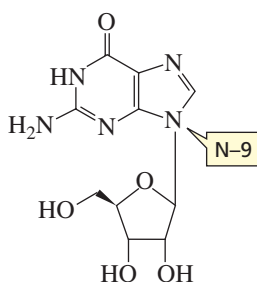
Nucleic acids are chains of five-membered-ring sugars linked by phosphate groups. Notice that the linkages are **phosphodiesters** (Figure 21.1). In RNA, the five-membered-ring sugar is D-ribose. In DNA, it is 2′-deoxy-D-ribose (D-ribose without an OH group in the 2′-position).

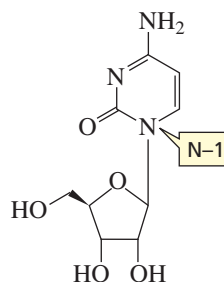
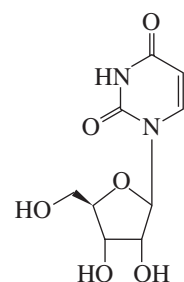
The anomeric carbon of each sugar is bonded to a nitrogen of a heterocyclic compound in a β-glycosidic linkage. (Recall from Section 16.6 that a β-linkage is one in which the substituent on C-1 of the furanose ring points up.) Because the heterocyclic compounds are amines, they are commonly referred to as **bases.**

▲ **Figure 21.1**
Nucleic acids consist of a chain of five-membered-ring sugars linked by phosphate groups. Each sugar (D-ribose in RNA, 2′-deoxy-D-ribose in DNA) is bonded to a heterocyclic amine (a base) in a β-glycosidic linkage.

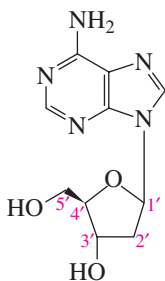
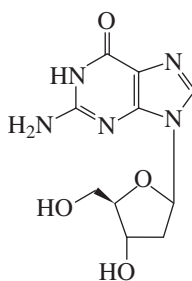
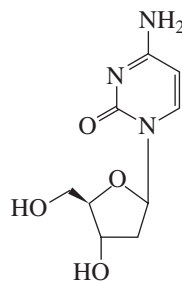
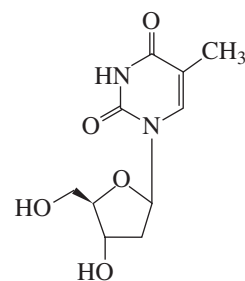
The vast differences in heredity between different species and between different members of the same species are determined by the sequence of the bases in DNA. Surprisingly, there are only four bases in DNA: two are substituted purines (adenine and guanine), and two are substituted pyrimidines (cytosine and thymine).

RNA also contains only four bases. Three (adenine, guanine, and cytosine) are the same as those in DNA, but the fourth base in RNA is uracil instead of thymine. Notice that thymine and uracil differ only by a methyl group. (Thymine is 5-methyluracil.) The reason DNA contains thymine instead of uracil is explained in Section 21.10.

The anomeric carbon of the furanose ring is bonded to purines at N-9 and to pyrimidines at N-1. A compound containing a base bonded to D-ribose or to 2′-deoxy-D-ribose is called a **nucleoside.** The ring positions of the sugar component of a nucleoside are indicated by primed numbers to distinguish them from the ring positions of the base. This is why the sugar component of DNA is referred to as 2′-deoxy-D-ribose.

nucleosides in RNA

Nucleoside = base + sugar

adenosine

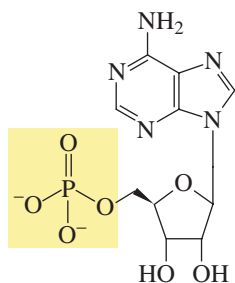
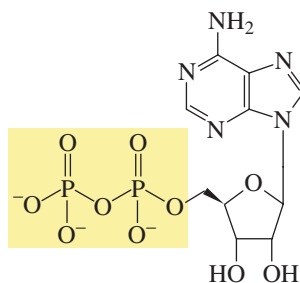
guanosine

cytidine

uridine

nucleosides in DNA

2′-deoxyadenosine

2′-deoxyguanosine

2′-deoxycytidine

thymidine

A **nucleotide** is a nucleoside with an OH group of the sugar bonded in an ester linkage to phosphoric acid. The nucleotides of RNA are more precisely called **ribonucleotides,** and those of DNA are called **deoxyribonucleotides.**

A nucleotide can exist as a monophosphate, a diphosphate, or a triphosphate. Nucleotides are named by adding *monophosphate*, *diphosphate,* or *triphosphate* to the name of the nucleoside.

nucleotides of adenosine

Nucleotide = base + sugar + phosphate

adenosine 5′-monophosphate
AMP

adenosine 5′-diphosphate
ADP

adenosine 5′-triphosphate
ATP

The names of the nucleotides are abbreviated (A, G, C, T, U—followed by MP, DP, or TP, depending on whether it is a monophosphate, diphosphate, or triphosphate—with a d in front if it contains 2′-deoxy-D-ribose instead of D-ribose: for example, ATP, dATP).

Notice the difference in the base names and their corresponding nucleoside (or nucleotide) names in Table 21.1. For example, adenine is the base, whereas adenosine is the nucleoside (or nucleotide); similarly, cytosine is the base, whereas cytidine is the nucleoside (or nucleotide), and so forth. Because uracil is found only in RNA, it is shown attached to D-ribose but not to 2'-deoxy-D-ribose; because thymine is found only in DNA, it is shown attached to 2'-deoxy-D-ribose but not to D-ribose.

Table 21.1 The Names of the Bases, the Nucleosides, and the Nucleotides

Base	Ribonucleoside	Deoxyribonucleoside	Ribonucleotide	Deoxyribonucleotide
Adenine	Adenosine	2′-Deoxyadenosine	Adenosine 5′-phosphate	2′-Deoxyadenosine 5′-phosphate
Guanine	Guanosine	2′-Deoxyguanosine	Guanosine 5′-phosphate	2′-Deoxyguanosine 5′-phosphate
Cytosine	Cytidine	2′-Deoxycytidine	Cytidine 5′-phosphate	2′-Deoxycytidine 5′-phosphate
Thymine	—	Thymidine	—	Thymidine 5′-phosphate
Uracil	Uridine	—	Uridine 5′-phosphate	

The Structure of DNA: Watson, Crick, Franklin, and Wilkins

Rosalind Franklin

James D. Watson was born in Chicago in 1928. He graduated from the University of Chicago at the age of 19 and received a Ph.D. three years later from Indiana University. In 1951, as a postdoctoral fellow at Cambridge University, Watson worked on determining the three-dimensional structure of DNA.

Francis H. C. Crick (1916–2004) was born in Northampton, England. Originally trained as a physicist, Crick did research on radar during World War II. After the war, deciding that the most interesting problem in science was the physical basis of life, he entered Cambridge University to study the structure of biological molecules by X-ray analysis. He was a graduate student when he carried out his portion of the work that led to the proposal of the double helical structure of DNA. He received a Ph.D. in chemistry in 1953.

Rosalind Franklin (1920–1958) was born in London. She graduated from Cambridge University and studied X-ray diffraction techniques in Paris. In 1951, she returned to England and accepted a position to develop an X-ray diffraction unit in the biophysics department at King's College. Her X-ray studies showed that DNA was a helix with the sugars and phosphate groups on the outside of the molecule. Tragically, Franklin never protected herself from her X-ray source and died without knowing the role her work had played in determining the structure of DNA, and without being recognized for her contribution.

Francis Crick (*left*) and James Watson (*right*)

Watson and Crick shared the 1962 Nobel Prize in Physiology or Medicine with Maurice Wilkins for determining the double-helical structure of DNA. Wilkins (1916–2004), who contributed X-ray studies that confirmed the double-helical structure, was born in New Zealand to Irish immigrants and moved to England six years later with his parents. He received a Ph.D. from Birmingham University. During World War II, he joined other British scientists who were working with American scientists on the development of the atomic bomb. He returned to England in 1945 and, having lost interest in physics, turned his attention to biology.

PROBLEM 1

Draw the structure for each of the following:

a. dCDP **c.** dUMP **e.** guanosine 5′-triphosphate
b. dTTP **d.** UDP **f.** adenosine 5′-monophosphate

21.2 NUCLEIC ACIDS ARE COMPOSED OF NUCLEOTIDE SUBUNITS

Nucleic acids are composed of long strands of nucleotide subunits (Figure 21.1). A **dinucleotide** contains two nucleotide subunits, an **oligonucleotide** contains 3–10 subunits, and a **polynucleotide** contains many subunits. DNA and RNA are polynucleotides.

Nucleoside triphosphates are the starting materials for the biosynthesis of nucleic acids. DNA is synthesized by enzymes called *DNA polymerases;* RNA is synthesized by enzymes called *RNA polymerases*. The nucleotides are linked as a result of an S_N2 reaction (Section 8.1): the 3′-OH group of one nucleoside triphosphate attacks the

α-phosphorus of another nucleoside triphosphate, breaking a phosphoanhydride bond and eliminating pyrophosphate (Figure 21.2). Thus, the phosphodiester joins the 3′-OH group of one nucleotide and the 5′-OH group of the next nucleotide, and the growing polymer is synthesized in the 5′ $\longrightarrow$ 3′ direction. In other words, new nucleotides are added to the 3′-end. Pyrophosphate is subsequently hydrolyzed, which makes the reaction irreversible (Section 20.2). Irreversibility is important if the genetic information in DNA is to be preserved. RNA strands are biosynthesized in the same way, using ribonucleoside triphosphates instead of 2′-deoxyribonucleoside triphosphates.

DNA is synthesized in the 5′ $\longrightarrow$ 3′ direction.

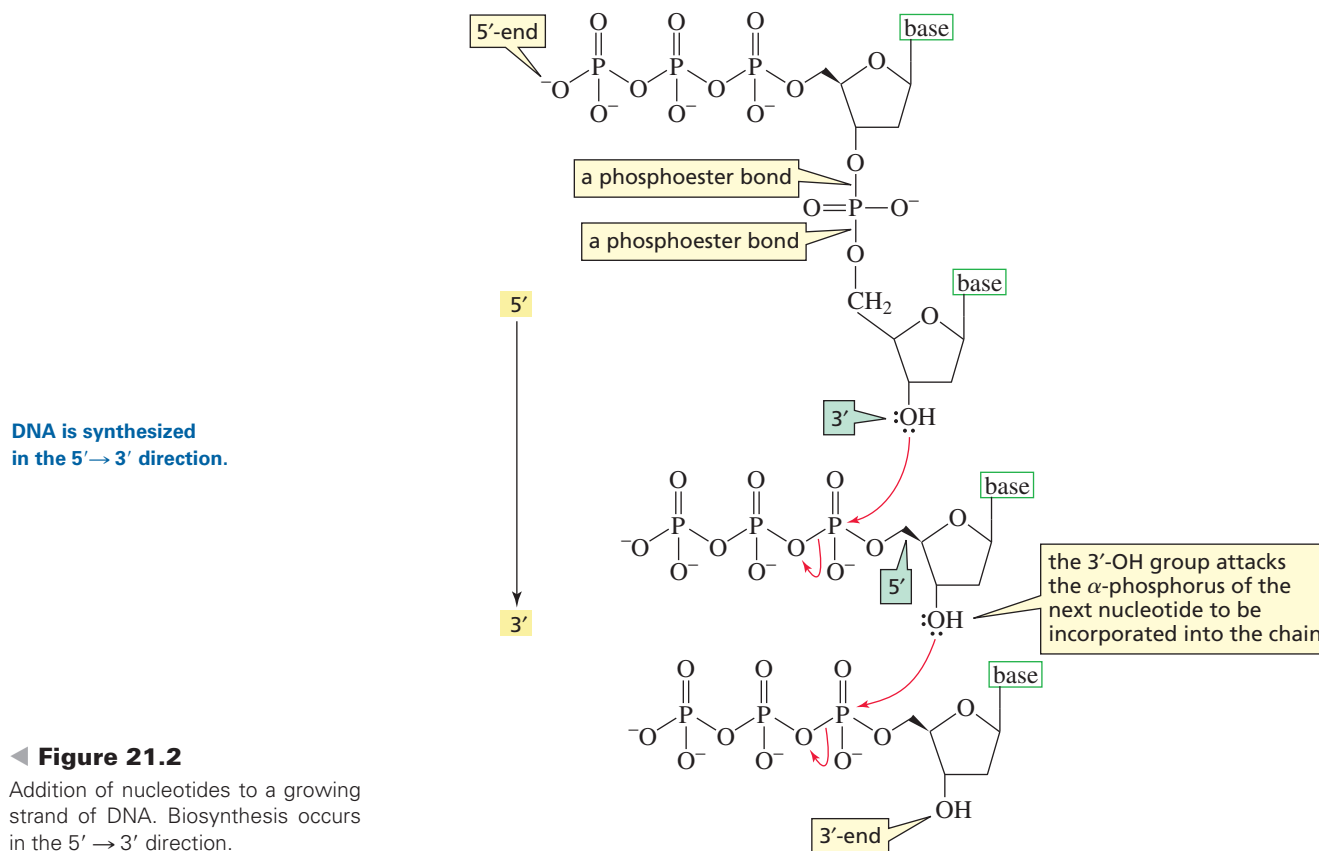



Figure 21.2
Addition of nucleotides to a growing strand of DNA. Biosynthesis occurs in the 5′ $\longrightarrow$ 3′ direction.

The **primary structure** of a nucleic acid is the sequence of bases in the strand. By convention, the sequence of bases is written in the 5′ $\longrightarrow$ 3′ direction (the 5′-end is on the left). Remember that the nucleotide at the 5′-end of the strand has an unlinked 5′-triphosphate group, and the nucleotide at the 3′-end has an unlinked 3′-hydroxyl group.

21.3 THE SECONDARY STRUCTURE OF DNA—THE DOUBLE HELIX

Watson and Crick, with the aid of Rosalind Franklin's X-ray data, concluded that DNA consists of two strands of nucleotides, with the sugar–phosphate backbone on the outside and the bases on the inside. The strands are antiparallel (they run in opposite directions) and are held together by hydrogen bonds between the bases on one strand and the bases on the other strand (Figure 21.3).

Adenine (A) always pairs with thymine (T), and guanine (G) always pairs with cytosine (C). This means the two strands are *complementary:* where there is an A in one strand, there is a T in the opposing strand; and where there is a G in one strand, there is a C in the other strand (Figure 21.3). Thus, if you know the sequence of bases in one strand, you can figure out the sequence of bases in the other strand.

Why does A pair with T? Why does G pair with C? First of all, the width of the double-stranded molecule is relatively constant, so a purine must pair with a pyrimidine. If the larger purines paired, the strands would bulge; if the smaller pyrimidines paired, the strands would have to pull in to bring the two pyrimidines close enough to form hydrogen bonds. But what causes A (a purine) to pair with T (a pyrimidine) rather than with C (the other pyrimidine)?

The base pairing is dictated by hydrogen bonding. Adenine forms two hydrogen bonds with thymine but would form only one hydrogen bond with cytosine. Guanine forms three hydrogen bonds with cytosine but would form only one hydrogen bond with thymine (Figure 21.4).

▲ **Figure 21.3**
The sugar–phosphate backbone of DNA is on the outside and the bases are on the inside; As pair with Ts and Gs pair with Cs. The two strands are antiparallel—that is, they run in opposite directions.

▲ **Figure 21.4**
Base pairing in DNA: adenine and thymine form two hydrogen bonds; cytosine and guanine form three hydrogen bonds.

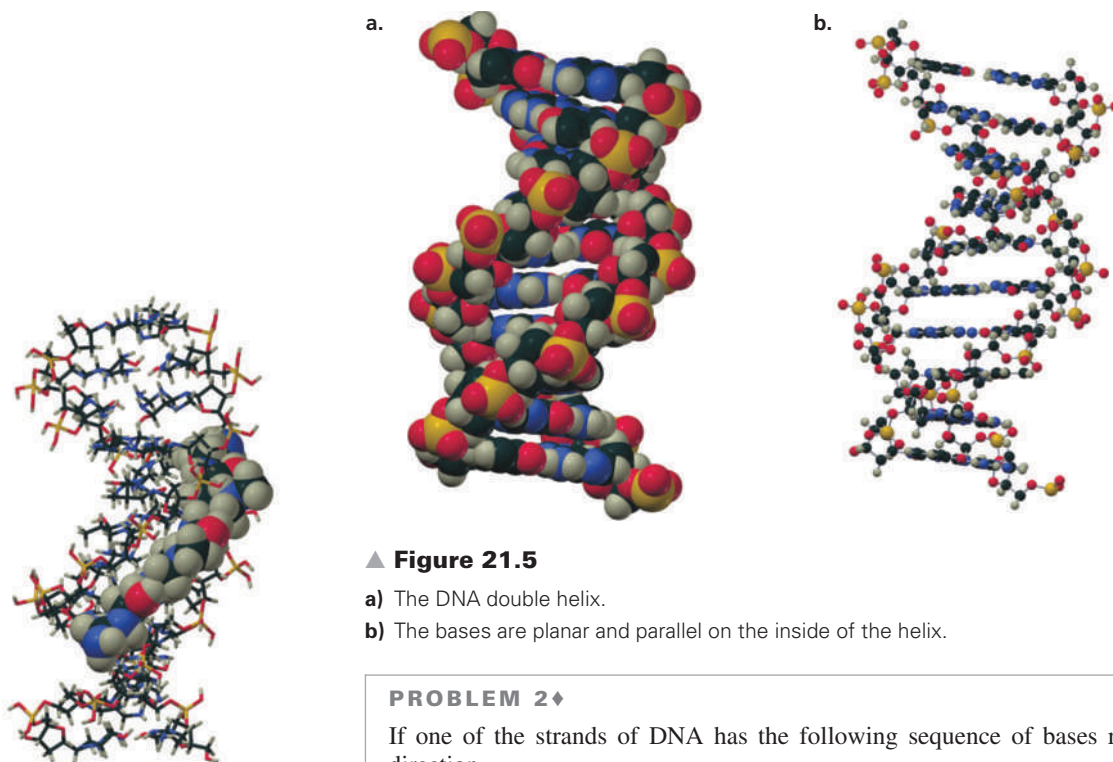
The two antiparallel DNA strands are not linear but are twisted into a helix around a common axis (Figure 21.5a). The base pairs are planar and parallel to each other on the inside of the helix (Figure 21.5b). The secondary structure is, therefore, known as a **double helix.** The double helix resembles a circular staircase: the base pairs are the rungs, and the sugar–phosphate backbones are the handrails (see pages 656 and 657). The negatively charged phosphates repel nucleophiles, thereby preventing cleavage of the phosphodiester bonds.

Hydrogen bonding between base pairs is just one of the forces holding the two strands of the DNA double helix together. The bases are planar aromatic molecules that stack on top of one another, each pair slightly rotated with respect to the next pair, like a partially spread-out hand of cards. In this arrangement, there are favorable van der Waals interactions between the mutually induced dipoles of adjacent pairs of bases. These interactions, known as **stacking interactions,** are weak attractive forces, but when added together they contribute significantly to the stability of the double helix.

There are two different alternating grooves in a DNA helix; a **major groove** and a narrower **minor groove.** Proteins and other molecules can bind to the grooves. The hydrogen-bonding properties of the functional groups facing into each groove determine what kind of molecules will bind to the groove. For example, netropsin is an antibiotic that works by binding to the minor groove of DNA (Figure 21.6).

▲ **Figure 21.5**

a) The DNA double helix.

b) The bases are planar and parallel on the inside of the helix.

▲ **Figure 21.6**

The antibiotic netropsin bound in the minor groove of DNA.

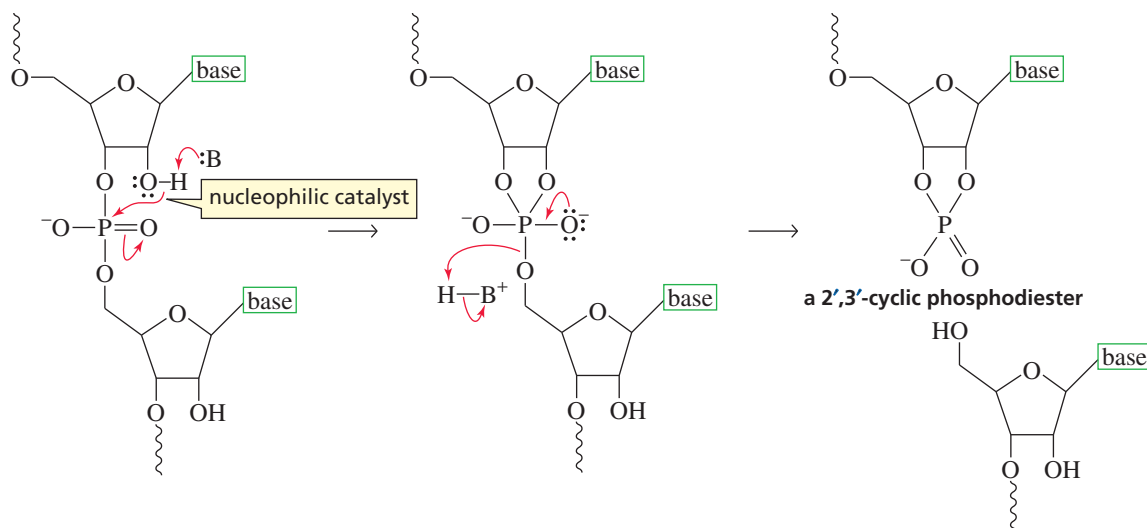
PROBLEM 2♦

If one of the strands of DNA has the following sequence of bases running in the 5′ → 3′ direction,

5′—G—G—A—C—A—A—T—C—T—G—C—3′

a. what is the sequence of bases in the complementary strand?
b. what base is closest to the 5′-end in the complementary strand?

21.4 WHY DNA DOES NOT HAVE A 2′-OH GROUP

Unlike DNA, RNA is not stable, because the 2′-OH group of ribose acts as a nucleophilic catalyst for the cleavage of RNA (Figure 21.7). This explains why the 2′-OH group is absent in DNA. DNA must remain intact throughout the life span of a cell in order to preserve the genetic information. Easy cleavage of DNA would have disastrous consequences for the cell and for life itself. RNA, in contrast, is synthesized as it is needed and is degraded once it has served its purpose.

▲ **Figure 21.7**

Catalysis of RNA cleavage by the 2′-OH group. RNA undergoes cleavage 3 billion times faster than DNA.

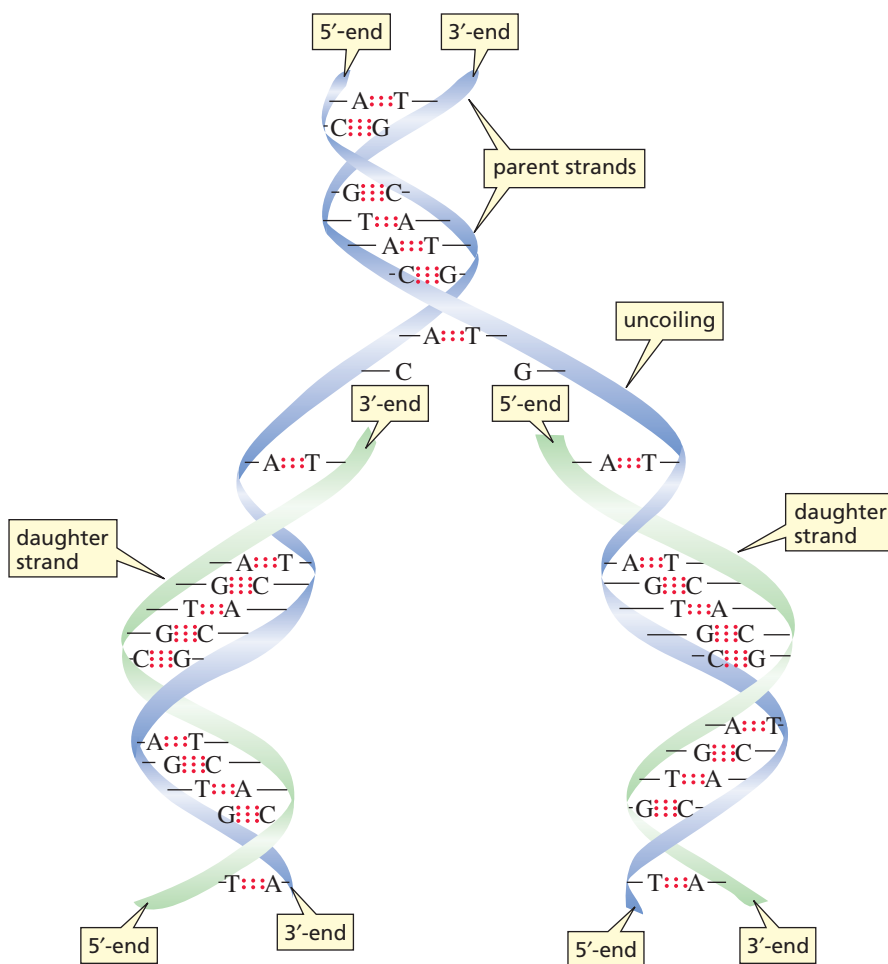
PROBLEM 3

The 2′,3′-cyclic phosphodiester that is formed (Figure 21.7) when RNA is cleaved reacts with water, forming a mixture of nucleotide 2′- and 3′-phosphates. Propose a mechanism for this reaction.

21.5 THE BIOSYNTHESIS OF DNA IS CALLED REPLICATION

The genetic information of a human cell is contained in 23 pairs of chromosomes. Each chromosome is composed thousands of **genes** (segments of DNA). The total DNA from a human cell—the **human genome**—contains 3.1 billion base pairs.

Part of the excitement created by Watson and Crick's proposed structure for DNA was due to the fact that the structure immediately suggested how DNA is able to pass on genetic information to succeeding generations. Because the two strands are complementary, both carry the same genetic information. Thus, when organisms reproduce, DNA molecules can be copied using the same base-pairing principle that is fundamental to their structure—that is, each strand can serve as the template for the synthesis of a complementary new strand (Figure 21.8). The new (daughter) DNA molecules are identical to the original (parent) molecule, so they contain all the original genetic information. The synthesis of identical copies of DNA is called **replication.**

All the reactions involved in nucleic acid synthesis are catalyzed by enzymes. The synthesis of DNA takes place in a region of the molecule where the strands have started to separate. Because a nucleic acid can be synthesized only in the $5' \rightarrow 3'$ direction, only the daughter strand on the left in Figure 21.8 is synthesized continuously in a single piece

▲ **Figure 21.8**

Replication of DNA. The green daughter strand on the left is synthesized continuously in the $5' \rightarrow 3'$ direction; the green daughter strand on the right is synthesized discontinuously in the $5' \rightarrow 3'$ direction.

(because it is synthesized in the 5′ ⟶ 3′ direction). The other daughter strand needs to grow in a 3′ ⟶ 5′ direction, so it is synthesized discontinuously in small pieces. Each piece is synthesized in the 5′ ⟶ 3′ direction, and the fragments are joined together by an enzyme called DNA ligase (see Figure 17.10 on page 601). Each of the two new molecules of DNA—called daughter molecules—contains one of the original parent strands (blue strand in Figure 21.8) plus a newly synthesized strand (green strand). This process is called **semiconservative replication.**

PROBLEM 4

Using a dark line for the original parental DNA and a wavy line for DNA synthesized from parental DNA, show what the population of DNA molecules would look like in the fourth generation. (Parental DNA is the first generation.)

21.6 DNA AND HEREDITY

If DNA contains hereditary information, there must be a method to decode that information. The decoding occurs in two steps.

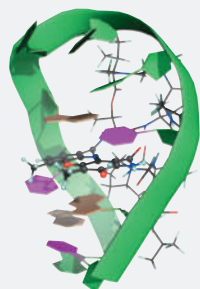
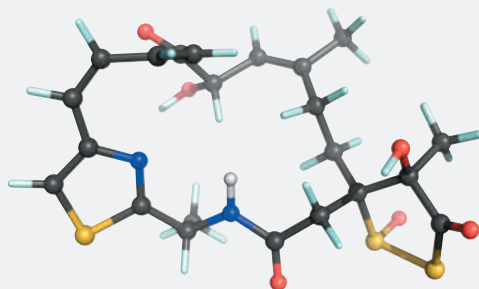
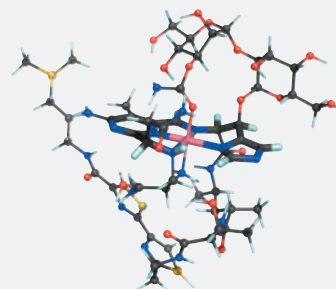
Transcription: DNA ⟶ RNA

Translation: mRNA ⟶ protein

1. The sequence of bases in DNA provides a blueprint for the synthesis of RNA; the synthesis of RNA from a DNA blueprint is called **transcription** (Section 21.7).
2. The sequence of bases in RNA determines the sequence of amino acids in a protein; the synthesis of a protein from an RNA blueprint is called **translation** (Section 21.9).

Do not confuse transcription and translation: these words are used just as they are used in English. Transcription (DNA to RNA) is copying *within the same language*—in this case the language of nucleotides. Translation (RNA to protein) is *changing to another language*—the language of amino acids. First, we will look at transcription.

Natural Products That Modify DNA

More than three-quarters of clinically approved anticancer drugs are natural products—compounds derived from plants, marine organisms, or microbes—that interact with DNA. Because cancer is characterized by the uncontrolled growth and proliferation of cells, compounds that interfere with the replication or transcription of DNA stop the growth of cancer cells. These drugs can interact with DNA by binding between the base pairs (called intercalation) or by binding to either its major or minor groove. The three anticancer drugs discussed here were isolated from *Streptomyces* bacteria found in soil.

actinomycin D

leinamycin

bleomycin

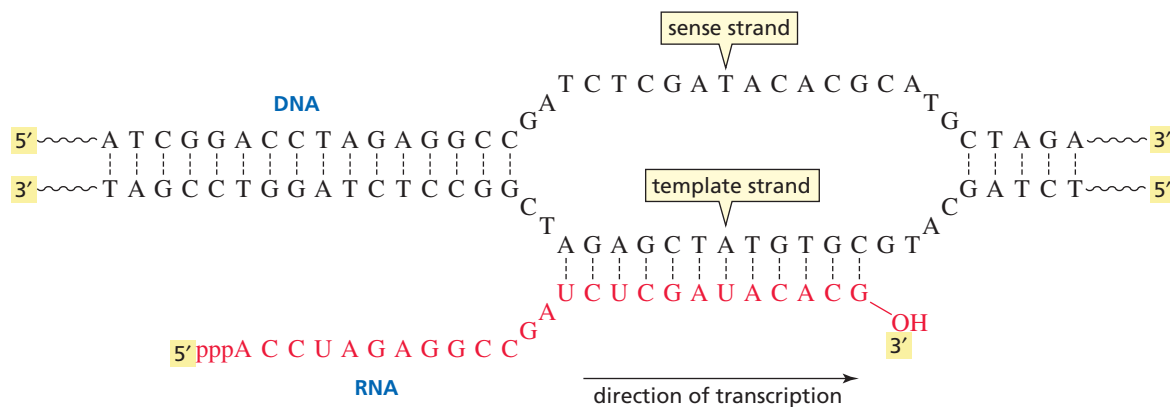
Because intercalating compounds become sandwiched between the stacked bases in DNA, they are planar and often aromatic. Their binding to DNA is stabilized by stacking interactions with neighboring base pairs. Actinomycin D is an example of an intercalator. When this drug binds to DNA, it distorts the double helix, inhibiting both the replication and transcription of DNA. Actinomycin D has been used to treat a variety of cancers.

Drugs that bind to the major and minor grooves of DNA do so by a combination of hydrogen bonding, van der Waals interactions, and electrostatic attractions—the same forces proteins use to bind their substrates. Leinamycin is an example of an anticancer drug that binds to the major groove. Once leinamycin is bound, it alkylates the N-7 position of a purine ring.

Bleomycin binds to the minor groove of DNA. Once in the minor groove, it uses a bound iron atom to remove a hydrogen atom from DNA, the first step in cleaving DNA. This drug has been approved for the treatment of Hodgkin lymphoma.

21.7 THE BIOSYNTHESIS OF RNA IS CALLED TRANSCRIPTION

Transcription starts when DNA unwinds at a particular site—called a *promoter site*—to form two single strands. One of the strands is called the **sense strand.** The complementary strand is called the **template strand.** In order for RNA to be synthesized in the $5' \rightarrow 3'$ direction, the template strand is read in the $3' \rightarrow 5'$ direction (Figure 21.9). The bases in the template strand specify the bases that need to be incorporated into RNA, following the same base-pairing principle used in the replication of DNA. For example, each guanine in the template strand specifies the incorporation of a cytosine into RNA, and each adenine in the template strand specifies the incorporation of a uracil into RNA. (Recall that in RNA, uracil is used instead of thymine.) Because both RNA and the sense strand of DNA are complementary to the template strand, RNA and the sense strand of DNA have the same base sequence, except that RNA has a uracil wherever the sense strand has a thymine. Just as there are promoter sites in DNA that signal where to start RNA synthesis, there are sites signaling that no more bases should be added to the growing RNA chain.

RNA is synthesized in the $5' \rightarrow 3'$ direction.

▲ Figure 21.9
Transcription: using DNA as a blueprint for the synthesis of RNA.

Until recently, it was thought that only about 2% of the DNA in our cells was used to make proteins and the rest had no informational content. However, our knowledge about DNA has been greatly expanded since the first human genome was sequenced in 2000. The biological purpose of about 80% of the DNA in the human genome had now been identified, and future experiments are expected to identify the purpose of the rest.

Apparently, a large amount of DNA is for the purpose of regulation. There are about 150 types of human cells, and each one carries the DNA that codes for 21,000 proteins. But only a subset of these is activated in a particular cell. For example, the gene that makes hair is not activated in a cell that makes insulin and vice versa.

It is now known that there are about 30,000 additional genes that are a blueprint for RNA that is not subsequently translated to make proteins. Instead, the RNA is used for regulation. In other words, these RNA strands appear to be the switches that turn genes on and off. The enormous number of switches has surprised scientists. Now the problem is to find out how these switches work.

PROBLEM 5♦

Why do both thymine and uracil specify the incorporation of adenine?

21.8 THE RNAs USED FOR PROTEIN BIOSYNTHESIS

RNA molecules are much shorter than DNA molecules and are generally single-stranded. While DNA molecules have billions of base pairs, RNA molecules rarely have more than 10,000 nucleotides. There are several kinds of RNA. The RNAs used for protein biosynthesis are as follows:

- **messenger RNA (mRNA),** whose sequence of bases determines the sequence of amino acids in a protein
- **ribosomal RNA (rRNA),** a structural component of ribosomes, which are the particles on which the biosynthesis of proteins takes place
- **transfer RNA (tRNA),** the carrier of amino acids used for protein synthesis

tRNA molecules are much smaller than mRNA or rRNA molecules. A tRNA contains only 70–90 nucleotides. The single strand of tRNA is folded into a characteristic cloverleaf structure, with three loops and a little bulge next to the right-hand loop (Figure 21.10a). There are at least four regions with complementary base pairing. The three bases at the bottom of the loop directly opposite the 5′- and 3′-ends are called an **anticodon.** All tRNAs have a CCA sequence at the 3′-end (Figures 21.10a and 21.10b).

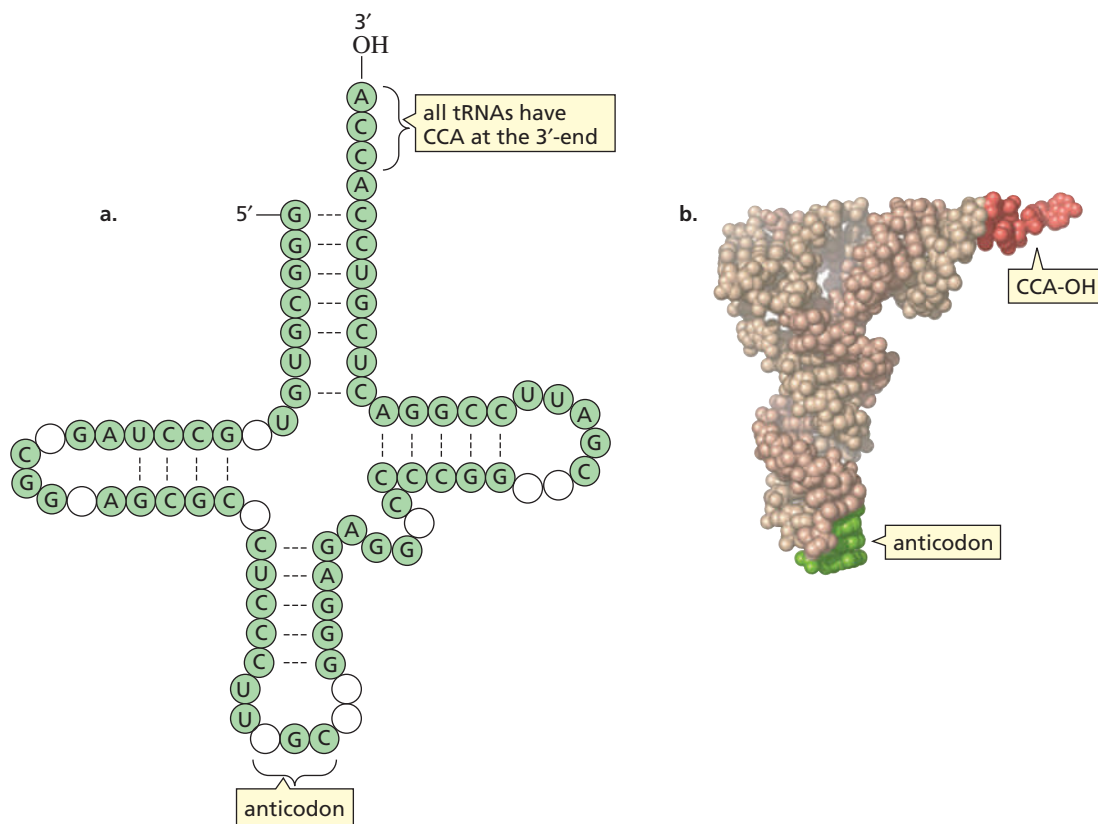



Figure 21.10

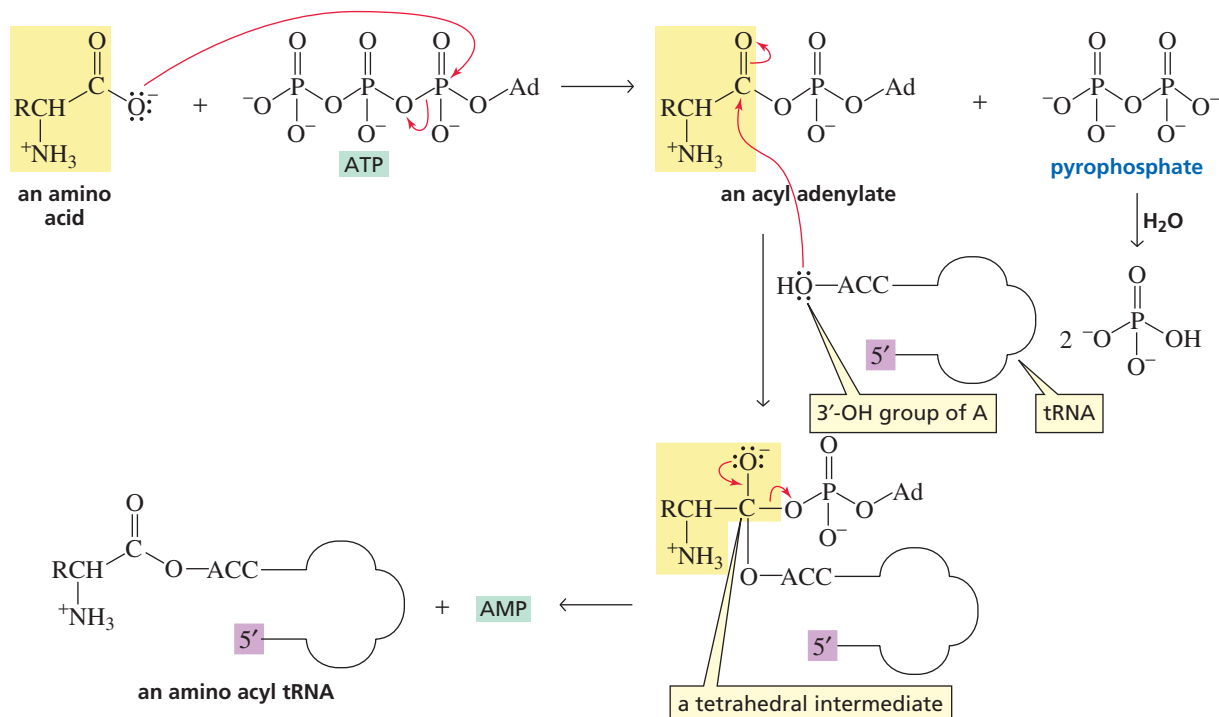
a) A transfer RNA: compared with other RNAs, tRNA contains a high percentage of unusual bases (shown as empty circles). These bases result from enzymatic modification of the four normal bases.

b) A transfer RNA: the anticodon is green; the CCA at the 3′-end is red.

Each tRNA can carry an amino acid bound as an ester to its terminal 3′-OH group. The amino acid will be inserted into a protein during protein biosynthesis. Each tRNA can carry only one particular amino acid. A tRNA that carries alanine is designated as $tRNA^{Ala}$.

The attachment of an amino acid to a tRNA is catalyzed by an enzyme called aminoacyl-tRNA synthetase. The mechanism for the reaction is shown here.

MECHANISM FOR THE ATTACHMENT OF AN AMINO ACID TO A tRNA

an amino acid
ATP
an acyl adenylate
pyrophosphate
H_2O
3′-OH group of A
tRNA
a tetrahedral intermediate
AMP
an amino acyl tRNA

- The carboxylate group of the amino acid is activated by forming an acyl adenylate; now the amino acid has a good leaving group (Section 11.16).
- The pyrophosphate that is eliminated is subsequently hydrolyzed, ensuring the irreversibility of the phosphoryl transfer reaction (Section 19.1).
- Notice that the second and third steps are the two steps of a nucleophilic acyl substitution reaction (Section 11.4). The 3′-OH group of tRNA adds to the carbonyl carbon of the acyl adenylate, forming a tetrahedral intermediate.
- The aminoacyl tRNA is formed when AMP is eliminated from the tetrahedral intermediate.

All the steps take place at the active site of the enzyme. Each amino acid has its own aminoacyl-tRNA synthetase. Each synthetase has two specific binding sites, one for the amino acid and one for the tRNA that will carry that amino acid (Figure 21.11).

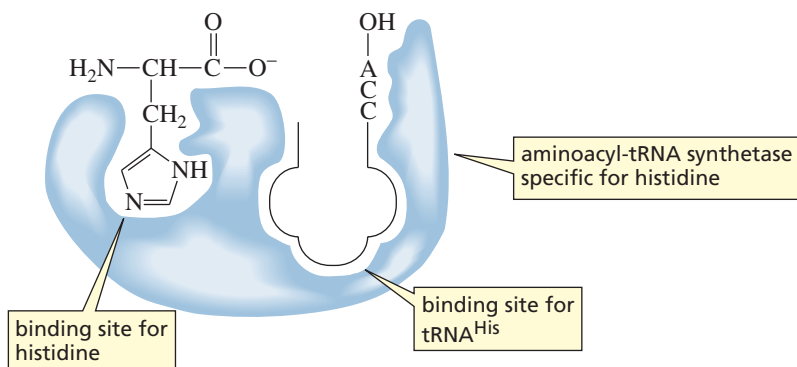



Figure 21.11 An aminoacyl-tRNA synthetase has a binding site for the amino acid and a binding site for the tRNA that will carry that amino acid. In this example, histidine is the amino acid, and $tRNA^{His}$ is the tRNA.

21.9 THE BIOSYNTHESIS OF PROTEINS IS CALLED TRANSLATION

A protein is biosynthesized from its N-terminal end to its C-terminal end by a process that reads the bases along the mRNA strand in the $5' \rightarrow 3'$ direction. The amino acid that is to be incorporated into a protein is specified by a three-base sequence called a **codon.** The bases are read consecutively and are never skipped. The three-base sequences and the amino acid that each sequence codes for are known as the **genetic code** (Table 21.2). A codon is written with the 5′-nucleotide on the left. For example, the codon UCA on mRNA codes for the amino acid serine, whereas CAG codes for glutamine.

Table 21.2 The Genetic Code

5′-Position	Middle position				3′-Position
	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Because there are four bases and the codons are triplets, 4^3 (or 64) different codons are possible. This is many more than are needed to specify the 20 different amino acids, so all the amino acids—except methionine and tryptophan—have more than one codon. It is not surprising, therefore, that methionine and tryptophan are the least abundant amino acids in proteins. Actually, 61 of the codons specify amino acids, and three codons are stop codons. **Stop codons** tell the cell to "stop protein synthesis here."

PROBLEM 6♦

If methionine is always the first amino acid incorporated into an oligopeptide, what oligopeptide is coded for by the following stretch of mRNA?

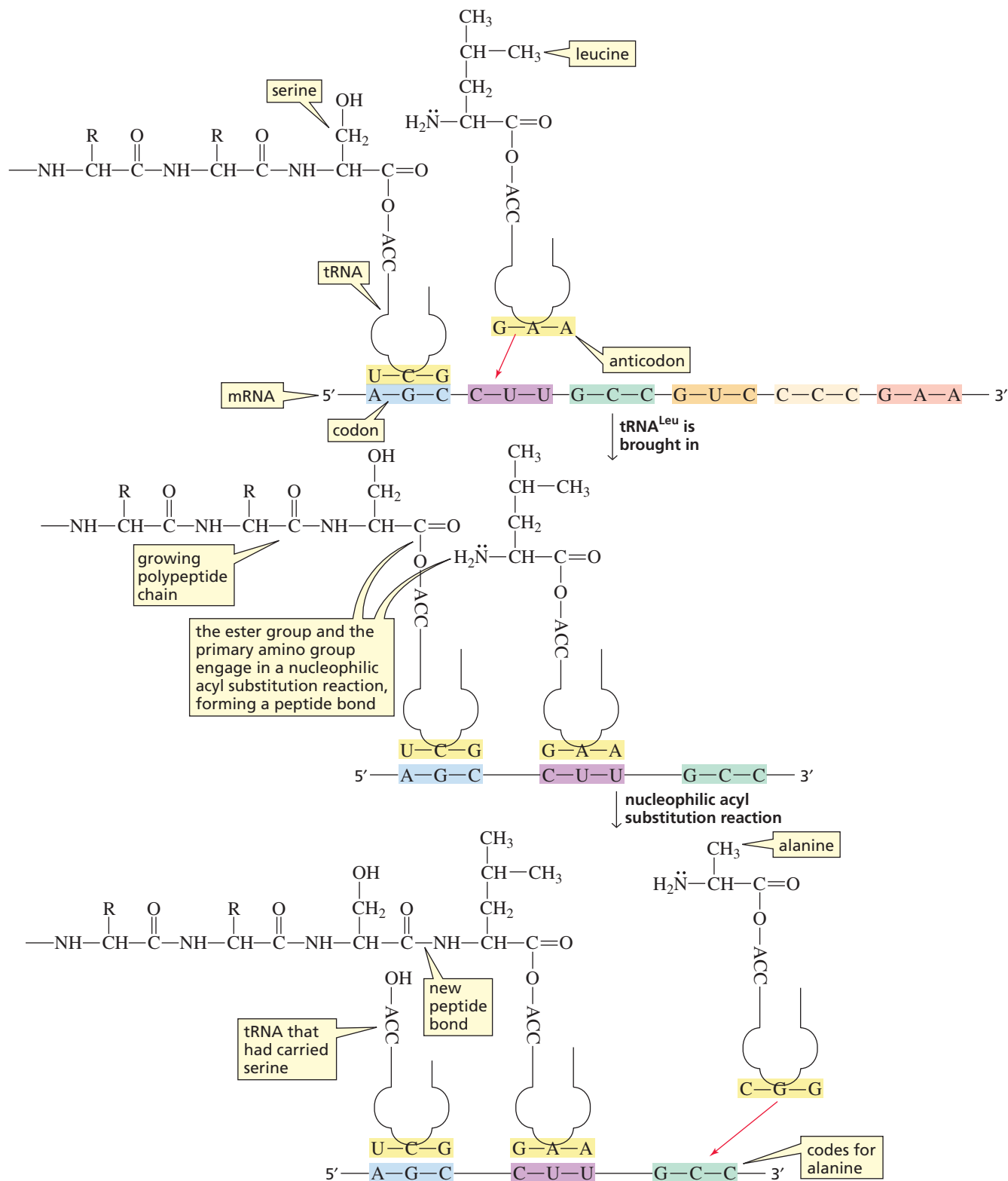
5′—G—C—A—U—G—G—A—C—C—C—C—G—U—U—A—U—U—A—A—A—C—A—C—3′

PROBLEM 7♦

Four Cs occur in a row in the segment of mRNA shown in Problem 6. What oligopeptide would be formed from the mRNA if one of the four Cs were cut out of the strand?

PROBLEM 8

UAA is a stop codon. Why does the UAA sequence in the segment of mRNA in Problem 6 not cause protein synthesis to stop?

How the information in mRNA is translated into a polypeptide is shown in Figure 21.12. In this figure, serine, specified by the codon AGC, was the last amino acid incorporated into the growing polypeptide chain.

▲ **Figure 21.12**
Translation: the sequence of bases in mRNA determines the sequence of amino acids in a protein.

- Serine was specified by the AGC codon in mRNA because the anticodon of the tRNA that carries serine is GCU (3′-UCG-5′). (Remember that a base sequence is read in the 5′ → 3′ direction, so the sequence of bases in an anticodon must be read from right to left.)
- The next codon, CUU, signals for a tRNA with an anticodon of AAG (3′-GAA-5′). That particular tRNA carries leucine. The amino group of leucine reacts in an enzyme-catalyzed nucleophilic acyl substitution reaction with the ester on the adjacent serine-carrying tRNA, displacing the tRNA that brought in serine (Section 11.4).
- The next codon (GCC) specifies a tRNA that carries alanine. The amino group of alanine will react in an enzyme-catalyzed nucleophilic acyl substitution reaction with the ester group on the adjacent leucine-carrying tRNA to displace the tRNA that brought in leucine.

A protein is biosynthesized in the N-terminal → C-terminal direction

Subsequent amino acids are brought in one at a time in the same way, with the codon in mRNA specifying the amino acid to be incorporated by complementary base pairing with the anticodon of the tRNA that carries that amino acid.

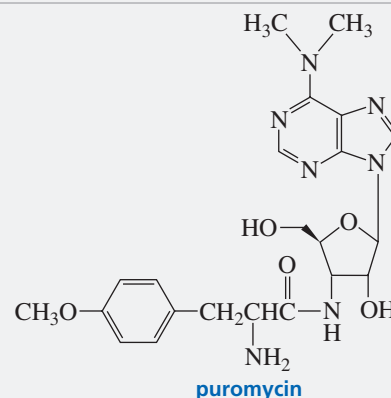
Sickle Cell Anemia

normal red blood cells

sickle red blood cell

Sickle cell anemia is an example of the damage that can be caused by a change in a single base of DNA (Problem 57 in Chapter 17). It is a hereditary disease caused when a GAG triplet becomes a GTG triplet in the sense strand of a section of DNA that codes for the β-subunit of hemoglobin (Section 17.13). As a consequence, the mRNA codon becomes GUG—which signals for incorporation of valine—rather than GAG, which would have signaled for incorporation of glutamate. The change from a polar glutamate to a nonpolar valine is sufficient to change the shape of the deoxyhemoglobin molecule. The change in shape stiffens the cells, making it difficult for them to squeeze through capillaries. Blockage of capillaries causes severe pain and can be fatal.

Antibiotics That Act by Inhibiting Translation

Puromycin is a naturally occurring antibiotic, one of several that acts by inhibiting translation. It does so by mimicking the 3′-CCA-aminoacyl portion of a tRNA, fooling the enzyme into transferring the growing peptide chain to the NH_2 group of puromycin rather than to the NH_2 group of the incoming 3′-CCA-aminoacyl tRNA. As a result, protein synthesis stops. Because puromycin blocks protein synthesis in eukaryotes as well as in prokaryotes, it is poisonous to humans and, therefore, is not a clinically useful antibiotic. To be clinically useful, an antibiotic must affect protein synthesis only in prokaryotic cells.

Clinically useful antibiotics	Mode of action
Tetracycline	Prevents the aminoacyl-tRNA from binding to the ribosome
Erythromycin	Prevents the incorporation of new amino acids into the protein
Streptomycin	Inhibits the initiation of protein synthesis
Chloramphenicol	Prevents the new peptide bond from being formed

puromycin

PROBLEM 9♦

A change in which base of a codon would be least likely to damage a protein?

PROBLEM 10♦

Write the sequences of bases in the sense strand of DNA that resulted in the mRNA in Problem 6.

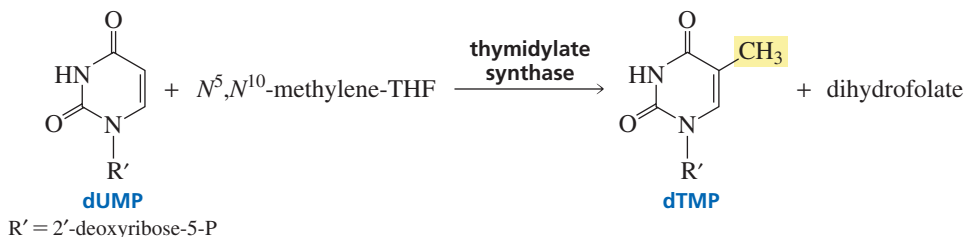
PROBLEM 11

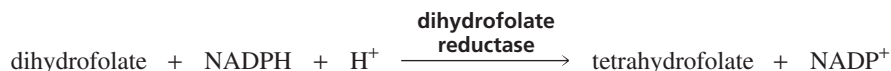
List the possible codons on mRNA that specify each amino acid in Problem 6 and the anticodon on the tRNA that carries that amino acid.

21.10 WHY DNA CONTAINS THYMINE INSTEAD OF URACIL

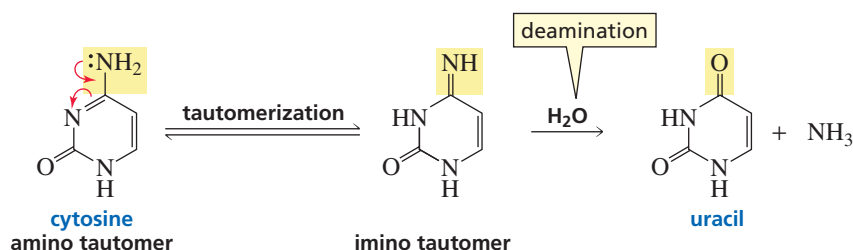
In Section 18.13, we saw that dTMP is formed by methylating dUMP, with coenzyme N^5,N^{10}-methylenetetrahydrofolate supplying the methyl group.

dUMP + N^5,N^{10}-methylene-THF $\xrightarrow{\text{thymidylate synthase}}$ dTMP + dihydrofolate

R′ = 2′-deoxyribose-5-P

Because the incorporation of the methyl group into uracil oxidizes tetrahydrofolate to dihydrofolate, dihydrofolate must be reduced back to tetrahydrofolate to prepare the coenzyme for another catalytic reaction. The reducing agent is NADPH.

$$\text{dihydrofolate} + \text{NADPH} + \text{H}^+ \xrightarrow{\text{dihydrofolate reductase}} \text{tetrahydrofolate} + \text{NADP}^+$$

The $NADP^+$ formed in this reaction has to be reduced back to NADPH by NADH. Every NADH formed in a cell can result in the formation of 2.5 ATPs (Section 19.3). Therefore, reducing dihydrofolate comes at the expense of ATP formation. This means that the synthesis of thymine is energetically expensive, so there must be a good reason for DNA to contain thymine instead of uracil.

The presence of thymine instead of uracil in DNA prevents potentially lethal mutations. Cytosine can tautomerize to form an imine (Section 13.3), which can be hydrolyzed to uracil (Section 12.8). The overall reaction is called a **deamination** because it removes an amino group.

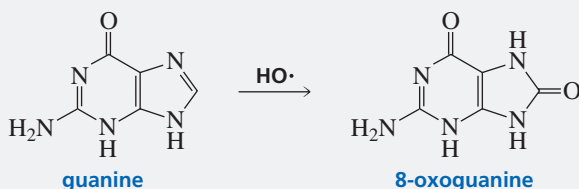
cytosine amino tautomer $\xrightleftharpoons{\text{tautomerization}}$ imino tautomer $\xrightarrow{H_2O}$ uracil + NH_3

(deamination)

If a C in DNA is deaminated to a U, the U will specify incorporation of an A into the daughter strand during replication instead of the G that would have been specified by C, and all the progeny of the daughter strand would have the same mutated chromosome. Fortunately, there is an enzyme that recognizes a U in DNA as a "mistake" and replaces it with a C before an incorrect base can be inserted into the daughter strand. The enzyme cuts out the U and replaces it with a C. If Us were normally found in DNA, the enzyme would not be able to distinguish between a normal U and a U formed by deamination of a cytosine. Having Ts in place of Us in DNA allows the Us that are found in DNA to be recognized as mistakes.

Unlike DNA that replicates itself, RNA is continually degraded and then resynthesized from the DNA template, so any mistake in RNA does not survive for long. Therefore, changing a C to a U in RNA could lead to some copies of a defective protein, but most would not be defective. Thus, it is not worth incurring the loss of ATP to incorporate Ts into RNA.

Antibiotics Act by a Common Mechanism

Recently, it has been found that three different classes of antibiotics (a β-lactam, a quinolone, and an aminoglycoside) all kill bacteria in the same way. The antibiotics trigger the production of hydroxide radicals. The hydroxide radicals oxidize guanines to 8-oxoguanines. The cell is able to recognize 8-oxoguanines as mistakes and replace them with guanines. However, if there are too many 8-oxoguanines in DNA, the cell's repair mechanism becomes overwhelmed. Then, instead of cutting out the 8-oxoguanines, it breaks the DNA strand, which leads to cell death.

guanine $\xrightarrow{HO\cdot}$ 8-oxoguanine

PROBLEM 12♦

Adenine can be deaminated to hypoxanthine, and guanine can be deaminated to xanthine. Draw structures for hypoxanthine and xanthine.

PROBLEM 13

Explain why thymine cannot be deaminated.

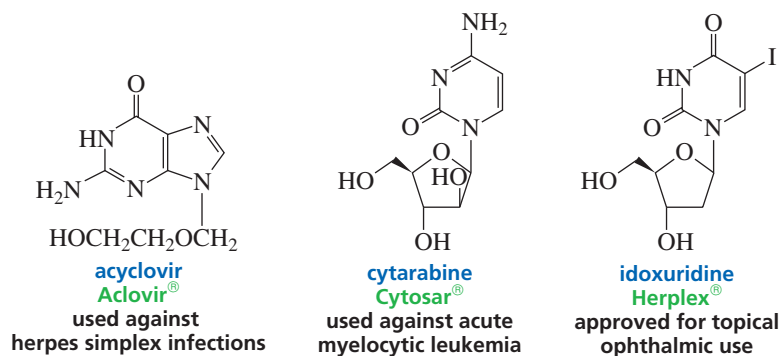
21.11 ANTIVIRAL DRUGS

Relatively few clinically useful drugs have been developed for viral infections. The slow progress of this endeavor is due to the nature of viruses and the way they replicate. Viruses are smaller than bacteria and consist of nucleic acid—either DNA or RNA—surrounded by a coat of protein. Some viruses penetrate the host cell; others merely inject their nucleic acid into the cell. In either case, the viral nucleic acid is transcribed by the host and is integrated into the host genome.

Most **antiviral drugs** are analogues of nucleosides, interfering with the virus's nucleic acid synthesis. In this way, they prevent the virus from replicating. For example, acyclovir, the drug used against herpes viruses, has a three-dimensional shape similar to that of guanine. Therefore, acyclovir can fool the virus into incorporating the drug instead of guanine into its DNA. Once this happens, the DNA strand can no longer grow because acyclovir lacks a ribose with a 3′-OH group.

acyclovir
Aclovir®
used against
herpes simplex infections

cytarabine
Cytosar®
used against acute
myelocytic leukemia

idoxuridine
Herplex®
approved for topical
ophthalmic use

Cytarabine, used for acute myelocytic leukemia, competes with cytosine for incorporation into viral DNA. Cytarabine contains an arabinose rather than a ribose (Table 16.1). Because the 2′-OH group is in the β-position, the bases in cytarabine-modified DNA are not able to stack properly (Section 21.3).

Idoxuridine is approved (in the United States) only for the topical treatment of ocular infections, although it is used for herpes infections in other countries. Idoxuridine has an iodo group in place of the methyl group of thymine and is incorporated into DNA in place of thymine. Chain elongation can continue because idoxuridine has a 3′-OH group, but the resulting DNA is more easily broken and is also not transcribed properly. (See also the description of AZT on page 672.)

Influenza Pandemics

Every year we face an outbreak of influenza (the flu). Most of the time it is a virus that is already present in the population and, therefore, can be controlled by flu shots. But every once in awhile, a new influenza virus appears, which can cause a worldwide pandemic because it is not affected by any immunity a person may have to older strains of influenza and can, therefore, spread rapidly and infect a large number of people. And almost no effective antiviral drugs are available for the flu. (See Tamiflu in Section 18.2.)

The Russian flu of 1889–1890 was the first of the flu pandemics. It killed about 1 million people. The Spanish flu that broke out in 1918–1919 killed over 50 million people worldwide. The Asian flu of 1956–1958 killed about 2 million people before a vaccine was developed in 1957 to contain it. The Hong Kong flu of 1968–1969—so called because it affected 15% of the population of Hong Kong—had a much lower death rate—only about 750,000 people died—because people who had had the Asian flu had some immunity. Because this was the last worldwide pandemic, public health officials worry that another may occur soon.

Recent flu outbreaks that have been causes for concern are the avian flu (bird flu), discovered in 1997, and the swine flu, discovered in 2009. The avian flu was linked to chickens, but it was subsequently transmitted to hundreds of people, 60% of whom died. The swine flu is a respiratory disease of pigs, but it has been known to affect people. There are concerns that either of these flus could become a worldwide pandemic.

The carbohydrates attached to the surface of the viral protein account for the biggest difference in virus strains. The symptoms caused by viruses that bind primarily to sugars in the nose and throat are not as severe as those caused by viruses that bind to sugars deep in the lungs.

21.12 HOW THE BASE SEQUENCE OF DNA IS DETERMINED

In June 2000, two teams of scientists (one from a private biotechnology company and one from the publicly funded Human Genome Project) announced that they had completed the first draft of the sequence of the 3.1 billion base pairs in human DNA. This was an enormous accomplishment.

Clearly, DNA molecules are too large to sequence as a unit. Therefore, DNA is first cleaved at specific base sequences, and the resulting DNA fragments are then sequenced individually.

restriction endonuclease	recognition sequence
*Alu*I	AG↓CT TC↑GA
*Fnu*DI	GG↓CC CC↑GG
*Pst*I	CTGCA↓G G↑ACGTC

The enzymes that cleave DNA at specific base sequences are called **restriction endonucleases,** and the DNA fragments they produce are called **restriction fragments.** Several hundred restriction endonucleases are now known; a few examples, the base sequence that each recognizes, and the point of cleavage in that base sequence are shown in the margin.

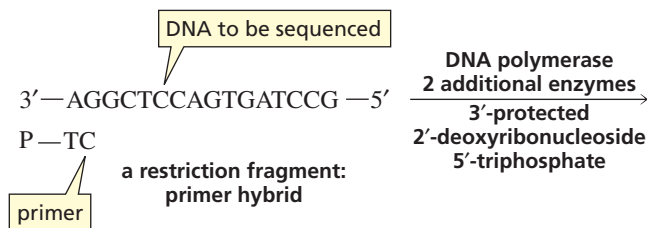
The base sequences that most restriction endonucleases recognize are *palindromes*. A palindrome is a word or a group of words that reads the same forward and backward. "Toot" and "race car" are examples of palindromes, as is "Was it a car or a cat I saw?" A restriction endonuclease recognizes a piece of DNA in which *the template strand is a palindrome of the sense strand*. In other words, the sequence of bases in the template strand (reading from right to left) is identical to the sequence of bases in the sense strand (reading from left to right).

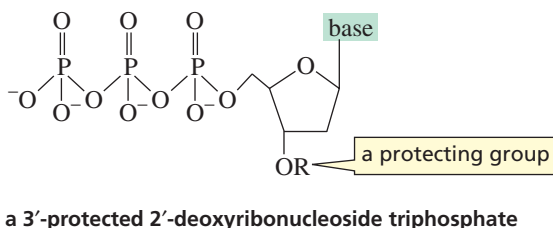
PROBLEM 14♦

Which of the following base sequences would most likely be recognized by a restriction endonuclease?

A ACGCGT **C** ACGGCA **E** ACATCGT
B ACGGGT **D** ACACGT **F** CCAACC

A currently used technique to determine the sequence of bases in DNA is an automated procedure called **pyrosequencing.** In this method, a small piece of DNA primer is added to the restriction fragment whose sequence is to be determined. Nucleotides are then added to the primer by base pairing with the restriction fragment. This method detects the identity of each base that adds to the primer.

Pyrosequencing requires DNA polymerase—the enzyme that adds nucleotides to a strand of DNA—and two additional enzymes that cause light to be emitted when pyrophosphate is detected.

Pyrosequencing also requires the four 2′-deoxyribonucleoside 5′-triphosphates, each with a protected 3′-OH group.

a 3′-protected 2′-deoxyribonucleoside triphosphate

The restriction fragment:primer hybrid is attached to a solid support in a column. The solid support is similar to the one used in ion-exchange chromatography (see Figure 17.4). The steps involved in pyrosequencing are as follows:

- The enzymes and one of the four 3′-protected 2′-deoxyribonucleoside 5′-triphosphates (for example, 3′-protected dATP) are added to the column.
- The reagents are washed from the solid support.
- The process is repeated with a different 3′-protected 2′-deoxynucleoside 5′-triphosphate (for example, 3′-protected dGTP).
- The process is repeated with 3′-protected dCTP, and then repeated again with 3′-protected dTTP.

- The sequencer keeps track of which of the four nucleotides caused light to be observed—in other words, which nucleotide released pyrophosphate as a result of being added to the primer.
- The protecting group on the 3′-OH is removed.

The steps are repeated to determine the identity of the next nucleotide that adds to the primer. Pyrosequencing can determine the base sequence of a restriction fragment with as many as 500 nucleotides.

When a human genome can be rapidly sequenced at a reasonable cost, the era of personalized medicine can begin. We will then understand what makes people more susceptible to certain diseases and why drugs work differently on different people. Eventually, drugs will be prescribed based on a patient's genetic profile.

21.13 GENETIC ENGINEERING

Genetic engineering (also called genetic modification) is the insertion of a segment of DNA into the replicating DNA of a host cell so that the segment of DNA is replicated along with the DNA of the host cell. Genetic engineering has many practical applications. For example, replicating the DNA that codes for human insulin makes it possible to synthesize large amounts of the protein (Section 17.8).

Agriculture is benefiting from genetic engineering as crops are being produced with new genes that increase their resistance to drought and insects. For example, genetically engineered cotton crops are resistant to the cotton bollworm, and genetically engineered corn is resistant to the corn rootworm. Genetically modified organisms (GMOs) have been responsible for a nearly 50% reduction in agricultural chemical sales in the United States. Recently, corn has been genetically modified to boost ethanol production, apples have been genetically modified to prevent them from turning brown when they are cut, and soybeans have been genetically modified to prevent trans fats from being formed when soybean oil is hydrogenated (Section 5.6).

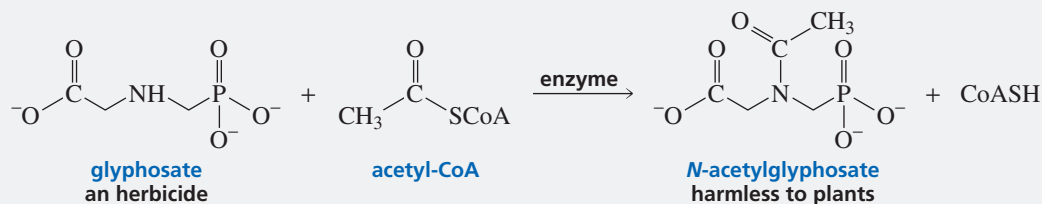
Resisting Herbicides

Glyphosate, the active ingredient in a well-known herbicide called Roundup, kills weeds by inhibiting an enzyme that plants need to synthesize phenylalanine and tryptophan, amino acids they require for growth. Corn and cotton have been genetically engineered to tolerate the herbicide. Then, when fields are sprayed with glyphosate, the weeds are killed but the crops are not.

These crops have been given a gene that produces an enzyme that uses acetyl-CoA to acetylate glyphosate in a nucleophilic acyl substitution reaction (Section 11.16). Unlike glyphosate, *N*-acetylglyphosate does not inhibit the enzyme that synthesizes phenylalanine and tryptophan.

Corn genetically engineered to resist the herbicide glyphosate by acetylating it.

$$^{-}O-C(=O)-CH_2-NH-CH_2-P(=O)(O^{-})-O^{-} + CH_3-C(=O)-SCoA \xrightarrow{\text{enzyme}} {}^{-}O-C(=O)-CH_2-N(C(=O)CH_3)-CH_2-P(=O)(O^{-})-O^{-} + CoASH$$

glyphosate an herbicide — **acetyl-CoA** — ***N*-acetylglyphosate** harmless to plants

Using Genetic Engineering to Treat the Ebola Virus

Plants have long been a source of drugs—morphine, digitoxin, and codeine are just a few examples (Section 9.10). Now scientists are attempting to obtain drugs from plants by biopharming. Biopharming uses genetic engineering techniques to produce drugs in crops such as corn, rice, tomatoes, and tobacco. To date, the only biopharmed drug approved by the Food and Drug Administration (FDA) is one that is manufactured in carrots and used to treat Gaucher's disease.

An experimental drug that was used to treat a handful of patients with Ebola, the virus that is spreading throughout West Africa, was obtained from genetically engineered tobacco plants. The tobacco plants were infected with three genetically engineered plant viruses that are harmless to humans and animals but have structures similar to that of the Ebola virus. As a result of being infected, the plants produced antibodies to the viruses. The antibodies were isolated from the plants, purified, and then used to treat the patients with Ebola.

The experimental drug had been tested in 18 monkeys who had been exposed to a lethal dose of Ebola. All 18 monkeys survived, whereas the three monkeys in the control group died. Typically, drugs go through rigorous testing on healthy humans prior to being administered to infected patients (see page 229). With the recent Ebola cases, the FDA made an exception because it feared that the drug might be these patients' only hope. Five of the seven people given the drug survived. Currently, it takes about 50 kilograms of tobacco leaves and about 4-6 months to produce enough drug to treat one patient.

tobacco plants

SOME IMPORTANT THINGS TO REMEMBER

- **Deoxyribonucleic acid (DNA)** encodes an organism's hereditary information and controls the growth and division of cells.
- A **nucleoside** contains a base bonded to D-ribose or to 2′-deoxy-D-ribose. A **nucleotide** is a nucleoside with an OH group of the sugar bonded to phosphoric acid by an ester linkage.
- **Nucleic acids** are composed of long strands of nucleotide subunits linked by phosphodiester bonds. These linkages join the 3′-OH group of one nucleotide to the 5′-OH group of the next nucleotide.
- DNA contains 2′-deoxy-D-ribose, whereas RNA contains D-ribose. The difference in the sugars causes DNA to be stable and RNA to be easily cleaved.
- The **primary structure** of a nucleic acid is the sequence of bases in its strand. DNA contains **A, G, C,** and **T;** RNA contains **A, G, C,** and **U.**
- The presence of **T** instead of **U** in DNA prevents mutations caused by tautomerization and imine hydrolysis of **C** to form **U**.
- DNA is double-stranded. The strands run in opposite directions and are twisted into a double helix, giving DNA a major groove and a minor groove.
- The bases are confined to the inside of the helix, and the sugar and phosphate groups are on the outside. The strands are held together by hydrogen bonds between bases of opposing strands as well as by **stacking interactions.**
- The two strands—one is called a **sense strand** and the other a **template strand**—are complementary: **A** pairs with **T,** and **G** pairs with **C.**
- DNA is synthesized in the $5' \rightarrow 3'$ direction by a process called **semiconservative replication.**
- The sequence of bases in DNA provides the blueprint for the synthesis (**transcription**) of RNA. RNA is synthesized in the $5' \rightarrow 3'$ direction by reading the bases along the DNA template strand in the $3' \rightarrow 5'$ direction.
- The RNAs used in protein biosynthesis are messenger RNA, ribosomal RNA, and transfer RNA.
- Each three-base sequence of mRNA—a **codon**—specifies the particular amino acid to be incorporated into a protein. The codons and the amino acids they specify are known as the **genetic code.**
- Protein synthesis (**translation**) proceeds from the N-terminal end to the C-terminal end by reading the bases along the mRNA strand in the $5' \rightarrow 3'$ direction.

- A tRNA carries the amino acid bound as an ester to its terminal 3′-position.
- Cytosines can be deaminated to uracils. **Deamination** is a reaction that removes an amino group.
- **Restriction endonucleases** cleave DNA at specific palindromes, forming **restriction fragments.**
- **Pyrosequencing** is a method used to determine the sequence of bases in the restriction fragments.
- A large amount of a particular protein can be synthesized by **genetic engineering.**
- The human genome contains 3.1 billion base pairs.

PROBLEMS

15. Draw structures for the following:
a. adenosine-5′-monophosphate **b.** uridine-5′-diphosphate **c.** ADP **d.** 2′-deoxycytidine

16. What would be the base sequence of the segment of DNA responsible for the biosynthesis of the following hexapeptide?

Met-Asp-Pro-Val-Ile-Lys-His

17. What is the sequence of bases in the template strand of DNA that codes for the mRNA in Problem 16?

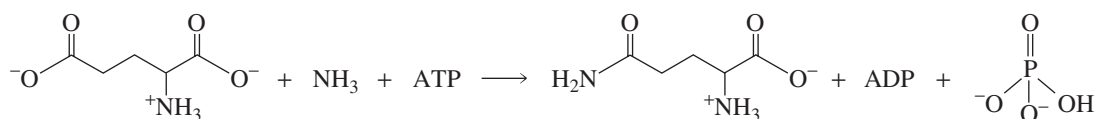
18. What is the sequence of bases in the sense strand of DNA that codes for the mRNA in Problem 16?

19. What would be the C-terminal amino acid if the codon at the 3′-end of the mRNA in Problem 16 underwent the following mutations?
a. The first base is changed to A. **c.** The third base is changed to A.
b. The second base is changed to A. **d.** The third base is changed to G.

20. What would be the base sequence of the segment of DNA responsible for the biosynthesis of the following hexapeptide?

Met-Asp-Pro-Val-Ile-Lys-His

21. Propose a mechanism for the following reaction:

$$^{-}OOC\text{-}CH_2CH_2CH(\overset{+}{N}H_3)\text{-}COO^{-} + NH_3 + ATP \longrightarrow H_2N\text{-}CO\text{-}CH_2CH_2CH(\overset{+}{N}H_3)\text{-}COO^{-} + ADP + {}^{-}O\text{-}P(=O)(O^{-})\text{-}OH$$

22. A segment of mRNA has 21 base pairs. It has 7 uracils in the segment.
a. How many thymines are in the segment? **b.** How many adenines are in the segment?

23. Match the codon with the anticodon:

Codon:	AAA	GCA	CUU	AGG	CCU	GGU	UCA	GAC
Anticodon:	ACC	CCU	UUU	AGG	UGA	AAG	GUC	UGC

24. Using the single-letter abbreviations for the amino acids in Table 17.2, write the sequence of amino acids in a tetrapeptide represented by the first four different letters in your first name. Do not use any letter twice. (Because not all letters are assigned to amino acids, you might have to use one or two letters in your last name.) Write one of the sequences of bases in mRNA that would result in the synthesis of that tetrapeptide. Write the sequence of bases in the sense strand of DNA that would result in formation of that fragment of mRNA.

25. Indicate whether each functional group of the five heterocyclic bases in nucleic acids can function as a hydrogen bond acceptor (A) or a hydrogen bond donor (D).

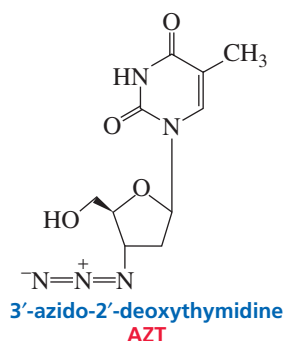
26. Using the A and D designations in Problem 25, indicate how base pairing would be affected if the bases existed in the enol form.

27. Which of the following pairs of dinucleotides are present in equal amounts in DNA?
A CC and GG **B** CG and GT **C** CA and TG **D** CG and AT **E** GT and CA **F** TA and AT

28. If an mRNA contained only U and G in random sequence, what amino acids would be present in the protein when the mRNA is translated?

29. Why is the codon a triplet rather than a doublet or a quartet?

30. Human immunodeficiency virus (HIV) is the retrovirus that causes AIDS. AZT was one of the first drugs designed to interfere with retroviral DNA synthesis. When cells take up AZT, they convert it to AZT-triphosphate. Explain how AZT interferes with DNA synthesis.

3′-azido-2′-deoxythymidine
AZT

31. The amino acid sequences of peptide fragments obtained from a normal protein were compared with those obtained from the same protein synthesized by a defective gene. They were found to differ in only one peptide fragment. Their amino acid sequences are shown here:

Normal: Gln-Tyr-Gly-Thr-Arg-Tyr-Val
Mutant: Gln-Ser-Glu-Pro-Gly-Thr

a. What is the defect in DNA?
b. It was later determined that the normal peptide fragment is an octapeptide with a C-terminal Val-Leu. What is the C-terminal amino acid of the mutant peptide?

32. Which cytosine in the following sense strand of DNA could cause the most damage to the organism if it were deaminated?

A—T—G—T—C—G—C—T—A—A—T—C

33. 5-Bromouracil, a highly mutagenic compound (that is, a compound that causes changes in DNA), is used in cancer chemotherapy. When administered to a patient, it is converted to the triphosphate and incorporated into DNA in place of thymine, which it resembles sterically. Why does it cause mutations? (*Hint:* The bromo substituent increases the stability of the enol tautomer.)

34. Why does DNA not unravel completely before replication begins?

35. The first amino acid incorporated into a polypeptide chain during its biosynthesis in prokaryotes is *N*-formylmethionine. Explain the purpose of the formyl group. (*Hint:* The ribosome has a binding site for the growing peptide chain and a binding site for the incoming amino acid.)

Appendix I

Physical Properties of Organic Compounds

Physical Properties of Alkenes

Name	Structure	mp (°C)	bp (°C)	Density (g/mL)
Ethene	$CH_2{=}CH_2$	–169	–104	
Propene	$CH_2{=}CHCH_3$	–185	–47	
1-Butene	$CH_2{=}CHCH_2CH_3$	–185	–6.3	
1-Pentene	$CH_2{=}CH(CH_2)_2CH_3$	–138	30	0.641
1-Hexene	$CH_2{=}CH(CH_2)_3CH_3$	–140	64	0.673
1-Heptene	$CH_2{=}CH(CH_2)_4CH_3$	–119	94	0.697
1-Octene	$CH_2{=}CH(CH_2)_5CH_3$	–101	122	0.715
1-Nonene	$CH_2{=}CH(CH_2)_6CH_3$	–81	146	0.730
1-Decene	$CH_2{=}CH(CH_2)_7CH_3$	–66	171	0.741
cis-2-Butene	*cis*-$CH_3CH{=}CHCH_3$	–180	37	0.650
trans-2-Butene	*trans*-$CH_3CH{=}CHCH_3$	–140	37	0.649
Methylpropene	$CH_2{=}C(CH_3)_2$	–140	–6.9	0.594
cis-2-Pentene	*cis*-$H_3CH{=}CHCH_2CH_3$	–180	37	0.650
trans-2-Pentene	*trans*-$CH_3CH{=}CHCH_2CH_3$	–140	37	0.649
Cyclohexene		–104	83	0.811

Physical Properties of Alkynes

Name	Structure	mp (°C)	bp (°C)	Density (g/mL)
Ethyne	$HC{\equiv}CH$	–82	–84.0	
Propyne	$HC{\equiv}CCH_3$	–101.5	–23.2	
1-Butyne	$HC{\equiv}CCH_2CH_3$	–122	8.1	
2-Butyne	$CH_3C{\equiv}CCH_3$	–32	27	0.694
1-Pentyne	$HC{\equiv}C(CH_2)_2CH_3$	–98	39.3	0.695
2-Pentyne	$CH_3C{\equiv}CCH_2CH_3$	–101	55.5	0.714
3-Methyl-1-butyne	$HC{\equiv}CCH(CH_3)_2$	–90	29	0.665
1-Hexyne	$HC{\equiv}C(CH_2)_3CH_3$	–132	71	0.715
2-Hexyne	$CH_3C{\equiv}C(CH_2)_2CH_3$	–92	84	0.731
3-Hexyne	$CH_3CH_2C{\equiv}CCH_2CH_3$	–101	81	0.725
1-Heptyne	$HC{\equiv}C(CH_2)_4CH_3$	–81	100	0.733
1-Octyne	$HC{\equiv}C(CH_2)_5CH_3$	–80	127	0.747
1-Nonyne	$HC{\equiv}C(CH_2)_6CH_3$	–50	151	0.757
1-Decyne	$HC{\equiv}C(CH_2)_7CH_3$	–44	174	0.766

Physical Properties of Cyclic Saturated Alkanes

Name	mp (°C)	bp (°C)	Density (g/mL)
Cyclopropane	–128	–33	
Cyclobutane	–80	–12	
Cyclopentane	–94	50	0.751
Cyclohexane	6.5	81	0.779
Cycloheptane	–12	118	0.811
Cyclooctane	14	149	0.834
Methylcyclopentane	–142	72	0.749
Methylcyclohexane	–126	100	0.769
cis-1,2-Dimethylcyclopentane	–62	99	0.772
trans-1,2-Dimethylcyclopentane	–120	92	0.750

Physical Properties of Ethers

Name	Structure	mp (°C)	bp (°C)	Density (g/mL)
Dimethyl ether	CH_3OCH_3	–141	–24.8	
Diethyl ether	$CH_3CH_2OCH_2CH_3$	–116	34.6	0.706
Dipropyl ether	$CH_3(CH_2)_2O(CH_2)_2CH_3$	–123	88	0.736
Diisopropyl ether	$(CH_3)_2CHOCH(CH_3)_2$	–86	69	0.725
Dibutyl ether	$CH_3(CH_2)_3O(CH_2)_3CH_3$	–98	142	0.764
Divinyl ether	$CH_2{=}CHOCH{=}CH_2$		35	
Diallyl ether	$CH_2{=}CHCH_2OCH_2CH{=}CH_2$		94	0.830
Tetrahydrofuran	(five-membered ring with O)	–108	66	0.889
Dioxane	(six-membered ring with two O)	12	101	1.034

Physical Properties of Alcohols

Name	Structure	mp (°C)	bp (°C)	Solubility (g/100 g H_2O at 25 °C)
Methanol	CH_3OH	–97.8	64	∞
Ethanol	CH_3CH_2OH	–114.7	78	∞
1-Propanol	$CH_3(CH_2)_2OH$	–127	97.4	∞
1-Butanol	$CH_3(CH_2)_3OH$	–90	118	7.9
1-Pentanol	$CH_3(CH_2)_4OH$	–78	138	2.3
1-Hexanol	$CH_3(CH_2)_5OH$	–52	157	0.6
1-Heptanol	$CH_3(CH_2)_6OH$	–36	176	0.2
1-Octanol	$CH_3(CH_2)_7OH$	–15	196	0.05
2-Propanol	$CH_3CHOHCH_3$	–89.5	82	∞
2-Butanol	$CH_3CHOHCH_2CH_3$	–115	99.5	12.5
2-Methyl-1-propanol	$(CH_3)_2CHCH_2OH$	–108	108	10.0
2-Methyl-2-propanol	$(CH_3)_3COH$	25.5	83	∞
3-Methyl-1-butanol	$(CH_3)_2CH(CH_2)_2OH$	–117	130	2
2-Methyl-2-butanol	$(CH_3)_2COHCH_2CH_3$	–12	102	12.5
2,2-Dimethyl-1-propanol	$(CH_3)_3CCH_2OH$	55	114	∞
Allyl alcohol	$CH_2{=}CHCH_2OH$	–129	97	∞
Cyclopentanol	C_5H_9OH	–19	140	s. sol.
Cyclohexanol	$C_6H_{11}OH$	24	161	s. sol.
Benzyl alcohol	$C_6H_5CH_2OH$	–15	205	4

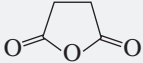
Physical Properties of Alkyl Halides

Name	bp (°C)			
	Fluoride	*Chloride*	*Bromide*	*Iodide*
Methyl	–78.4	–24.2	3.6	42.4
Ethyl	–37.7	12.3	38.4	72.3
Propyl	–2.5	46.6	71.0	102.5
Isopropyl	–9.4	34.8	59.4	89.5
Butyl	32.5	78.4	100	130.5
Isobutyl		68.8	90	120
sec-Butyl		68.3	91.2	120.0
tert-Butyl		50.2	73.1	dec.
Pentyl	62.8	108	130	157.0
Hexyl	92	133	154	179

Physical Properties of Amines

Name	Structure	mp (°C)	bp (°C)	Solubility (g/100 g H_2O at 25 °C)
Primary Amines				
Methylamine	CH_3NH_2	–93	–6.3	v. sol.
Ethylamine	$CH_3CH_2NH_2$	–81	17	∞
Propylamine	$CH_3(CH_2)_2NH_2$	–83	48	∞
Isopropylamine	$(CH_3)_2CHNH_2$	–95	33	∞
Butylamine	$CH_3(CH_2)_3NH_2$	–49	78	v. sol.
Isobutylamine	$(CH_3)_2CHCH_2NH_2$	–85	68	∞
sec-Butylamine	$CH_3CH_2CH(CH_3)NH_2$	–72	63	∞
tert-Butylamine	$(CH_3)_3CNH_2$	–67	46	∞
Cyclohexylamine	$C_6H_{11}NH_2$	–18	134	s. sol.
Secondary Amines				
Dimethylamine	$(CH_3)_2NH$	–93	7.4	v. sol.
Diethylamine	$(CH_3CH_2)_2NH$	–93	55	10.0
Dipropylamine	$(CH_3CH_2CH_2)_2NH$	–50	110	10.0
Dibutylamine	$(CH_3CH_2CH_2CH_2)_2NH$	–62	159	s. sol.
Tertiary Amines				
Trimethylamine	$(CH_3)_3N$	–115	2.9	91
Triethylamine	$(CH_3CH_2)_3N$	–114	89	14
Tripropylamine	$(CH_3CH_2CH_2)_3N$	–93	157	s. sol.

Physical Properties of Benzene and Substituted Benzenes

Name	Structure	mp (°C)	bp (°C)	Solubility (g/100 g H_2O at 25 °C)
Aniline	$C_6H_5NH_2$	–6	184	3.7
Benzene	C_6H_6	5.5	80.1	s. sol.
Benzaldehyde	C_6H_5CHO	–26	178	s. sol.
Benzamide	$C_6H_5CONH_2$	132	290	s. sol.
Benzoic acid	C_6H_5COOH	122	249	0.34
Bromobenzene	C_6H_5Br	–30.8	156	insol.
Chlorobenzene	C_6H_5Cl	–45.6	132	insol.
Nitrobenzene	$C_6H_5NO_2$	5.7	210.8	s. sol.
Phenol	C_6H_5OH	43	182	s. sol.
Styrene	$C_6H_5CH{=}CH_2$	–30.6	145.2	insol.
Toluene	$C_6H_5CH_3$	–95	110.6	insol.

Physical Properties of Carboxylic Acids

Name	Structure	mp (°C)	bp (°C)	Solubility (g/100 g H_2O at 25 °C)
Formic acid	$HCOOH$	8.4	101	∞
Acetic acid	CH_3COOH	16.6	118	∞
Propionic acid	CH_3CH_2COOH	–21	141	∞
Butanoic acid	$CH_3(CH_2)_2COOH$	–5	162	∞
Pentanoic acid	$CH_3(CH_2)_3COOH$	–34	186	4.97
Hexanoic acid	$CH_3(CH_2)_4COOH$	–4	202	0.97
Heptanoic acid	$CH_3(CH_2)_5COOH$	–8	223	0.24
Octanoic acid	$CH_3(CH_2)_6COOH$	17	237	0.068
Nonanoic acid	$CH_3(CH_2)_7COOH$	15	255	0.026
Decanoic acid	$CH_3(CH_2)_8COOH$	32	270	0.015

Physical Properties of Dicarboxylic Acids

Name	Structure	mp (°C)	Solubility (g/100 g H_2O at 25 °C)
Oxalic acid	$HOOCCOOH$	189	s
Malonic acid	$HOOCCH_2COOH$	136	v. sol.
Succinic acid	$HOOC(CH_2)_2COOH$	185	s. sol.
Glutaric acid	$HOOC(CH_2)_3COOH$	98	v. sol.
Adipic acid	$HOOC(CH_2)_4COOH$	151	s. sol.
Pimelic acid	$HOOC(CH_2)_5COOH$	106	s. sol.
Phthalic acid	1,2-$C_6H_4(COOH)_2$	231	s. sol.
Maleic acid	*cis*-$HOOCCH{=}CHCOOH$	130.5	v. sol.
Fumaric acid	*trans*-$HOOCCH{=}CHCOOH$	302	s. sol.

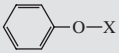
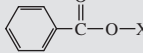
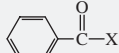
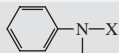
Physical Properties of Acyl Chlorides and Acid Anhydrides

Name	Structure	mp (°C)	bp (°C)
Acetyl chloride	CH_3COCl	–112	51
Propionyl chloride	CH_3CH_2COCl	–94	80
Butyryl chloride	$CH_3(CH_2)_2COCl$	–89	102
Valeryl chloride	$CH_3(CH_2)_3COCl$	–110	128
Acetic anhydride	$CH_3(CO)O(CO)CH_3$	–73	140
Succinic anhydride	(ring structure: O=C–O–C=O five-membered ring) O O O	120	261

Physical Properties of Esters

Name	Structure	mp (°C)	bp (°C)
Methyl formate	$HCOOCH_3$	–100	32
Ethyl formate	$HCOOCH_2CH_3$	–80	54
Methyl acetate	CH_3COOCH_3	–98	57.5
Ethyl acetate	$CH_3COOCH_2CH_3$	–84	77
Propyl acetate	$CH_3COO(CH_2)_2CH_3$	–92	102
Methyl propionate	$CH_3CH_2COOCH_3$	–87.5	80
Ethyl propionate	$CH_3CH_2COOCH_2CH_3$	–74	99
Methyl butyrate	$CH_3CH_2CH_2COOCH_3$	–84.8	102.3
Ethyl butyrate	$CH_3CH_2CH_2COOCH_2CH_3$	–93	121

Physical Properties of Amides

Name	Structure	mp (°C)	bp (°C)
Formamide	$HCONH_2$	3	200 d*
Acetamide	CH_3CONH_2	82	221
Propanamide	$CH_3CH_2CONH_2$	80	213
Butanamide	$CH_3(CH_2)_2CONH_2$	116	216
Pentanamide	$CH_3(CH_2)_3CONH_2$	106	232

*d means the substance decomposes.

Physical Properties of Aldehydes

Name	Structure	mp (°C)	bp (°C)	Solubility (g/100 g H_2O at 25 °C)
Formaldehyde	$HCHO$	–92	–21	v. sol.
Acetaldehyde	CH_3CHO	–121	21	∞
Propionaldehyde	CH_3CH_2CHO	–81	49	16
Butyraldehyde	$CH_3(CH_2)_2CHO$	–96	75	7
Pentanal	$CH_3(CH_2)_3CHO$	–92	103	s. sol.
Hexanal	$CH_3(CH_2)_4CHO$	–56	131	s. sol.
Heptanal	$CH_3(CH_2)_5CHO$	–43	153	0.1
Octanal	$CH_3(CH_2)_6CHO$		171	insol.
Nonanal	$CH_3(CH_2)_7CHO$		192	insol.
Decanal	$CH_3(CH_2)_8CHO$	–5	209	insol.
Benzaldehyde	C_6H_5CHO	–26	178	0.3

Physical Properties of Ketones

Name	Structure	mp (°C)	bp (°C)	Solubility (g/100 g H_2O at 25 °C)
Acetone	CH_3COCH_3	–95	56	∞
2-Butanone	$CH_3COCH_2CH_3$	–86	80	25.6
2-Pentanone	$CH_3CO(CH_2)_2CH_3$	–78	102	5.5
2-Hexanone	$CH_3CO(CH_2)_3CH_3$	–57	127	1.6
2-Heptanone	$CH_3\ CO(CH_2)_4CH_3$	–36	151	0.4
2-Octanone	$CH_3CO(CH_2)_5CH_3$	–16	173	insol.
2-Nonanone	$CH_3CO(CH_2)_6CH_3$	–7	195	insol.
2-Decanone	$CH_3CO(CH_2)_7CH_3$	14	210	insol.
3-Pentanone	$CH_3CH_2COCH_2CH_3$	–40	102	4.8
3-Hexanone	$CH_3CH_2CO(CH_2)_2CH_3$		123	1.5
3-Heptanone	$CH_3CH_2CO(CH_2)_3CH_3$	–39	149	0.3
Acetophenone	$CH_3COC_6H_5$	19	202	insol.
Propiophenone	$CH_3CH_2COC_6H_5$	18	218	insol.

Appendix II

[1]H NMR Chemical Shifts

I X = CH_3 ∘∘ X = CH_2—   •• X = CH—

(ppm) 5 4 3 2 1 0

RCH$_2$—X

RCH=CH—X

RC≡C—X

C_6H_5—X

F—X

Cl—X

Br—X

I—X

HO—X

RO—X

C_6H_5—O—X

R—C(=O)—O—X

C_6H_5—C(=O)—O—X

H—C(=O)—X

R—C(=O)—X

C_6H_5—C(=O)—X

HO—C(=O)—X

RO—C(=O)—X

R$_2$N—C(=O)—X

N≡C—X

H$_2$N—X

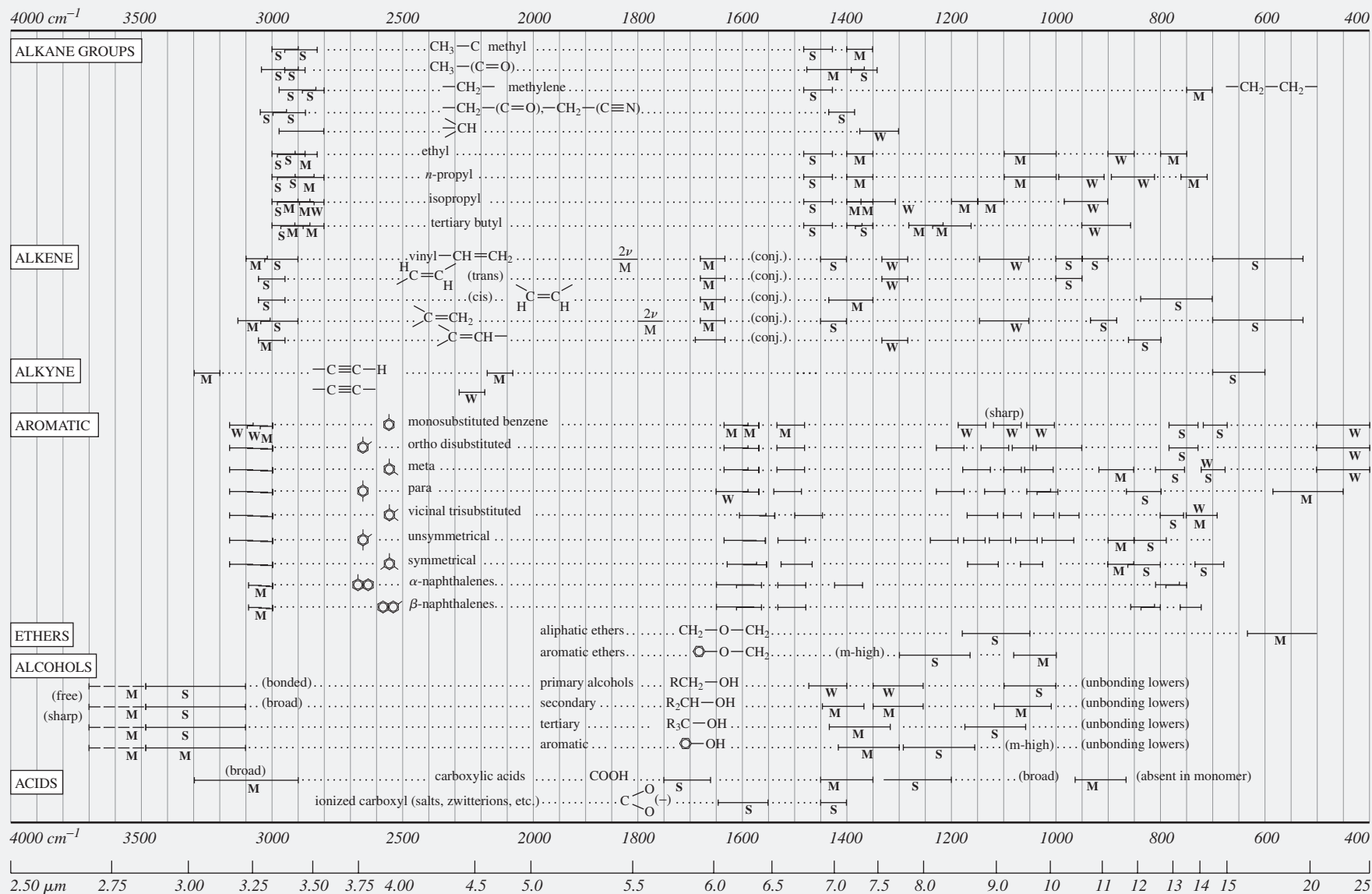
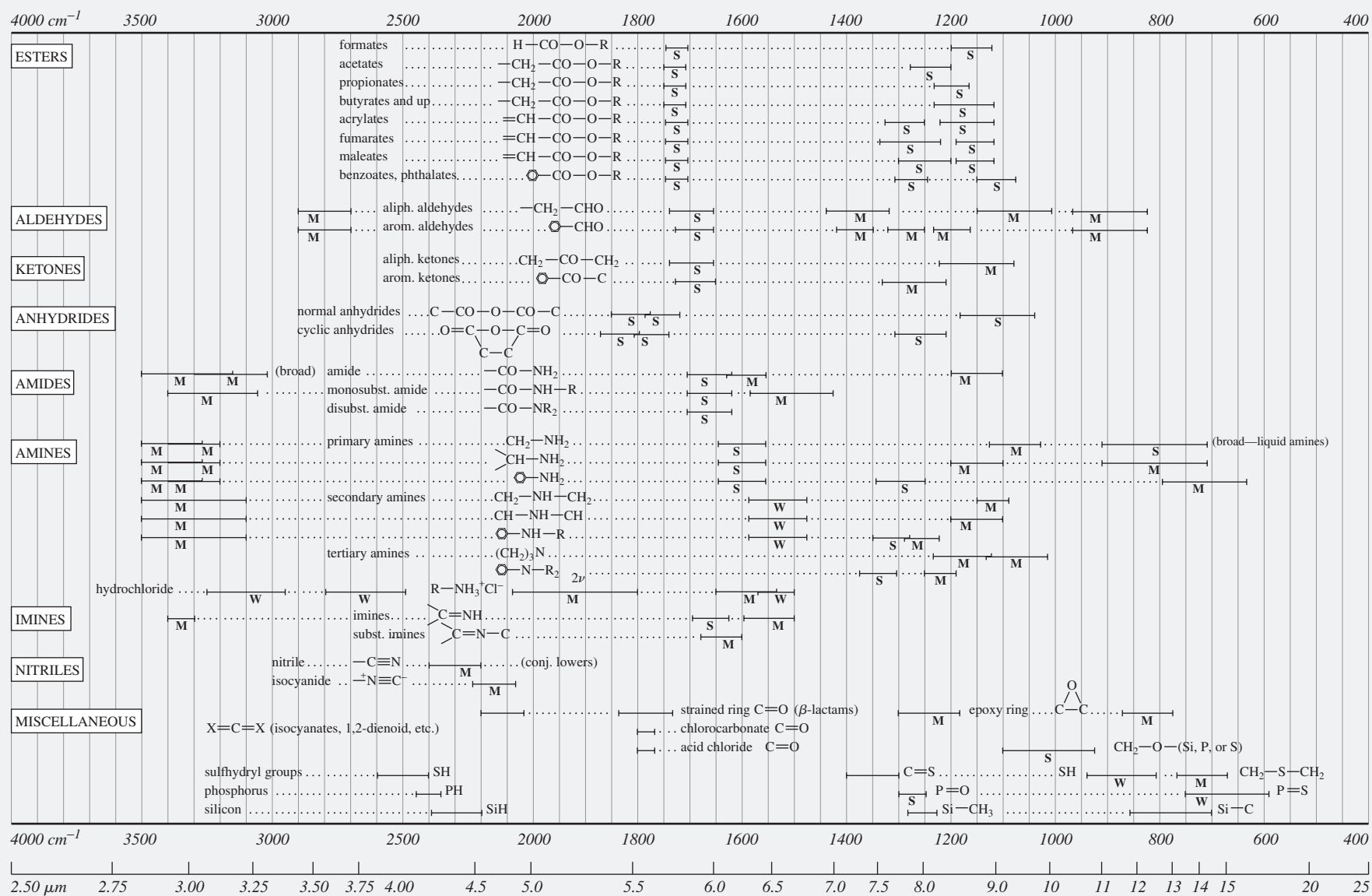
R$_2$N—X

C_6H_5—N(R)—X

R$_3\overset{+}{N}$—X

R—C(=O)—NH—X

O$_2$N—X

Characteristic Infrared Group Frequencies (S = strong, M = medium, W = weak). (Courtesy of N.B. Colthup, Stamford Research Laboratories, American Cyanamid Company, and the editor of the *Journal of the Optical Society*.) Overtone bands are marked 2ν.

Characteristic Infrared Group Frequencies (continued)

(continued)

Characteristic Infrared Group Frequencies (continued)
4000 cm^{-1} 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400
fluorine
fluorine
fluorine
chlorine
chlorine
bromine
CF_2 and CF_3
C—F (unsat.)
C—F (sat.)
2ν
CCl_2 and CCl_3
CCl (aliph.)
CBr_2 and CBr_3
CBr (aliph.)
INORGANIC SALTS AND DERIVED COMPOUNDS
sulfur–oxygen compounds
ionic sulfate $(SO_4)^{2-}$
ionic sulfonate $R—SO_3^-$
sulfonic acid $R—SO_3H$
covalent sulfate $R—O—SO_2—O—R$
covalent sulfonate $R—O—SO_2—R$
sulfonamide $R—SO_2—NH_2$
sulfone $R—SO_2—R$
sulfoxide R—SO—R
phosphorus–oxygen
ionic phosphate $(PO_4)^{3-}$
covalent phosphate $(RO)_3P\rightarrow O$ $CH_2—O—P\rightarrow O$
covalent phosphate ⌬—O—P—O
carbon–oxygen
ionic carbonate $(CO_3)^{2-}$
covalent carbonate $O{=}C(O—R_2)$
imino carbonate $HN{=}C(O—R_2)$
nitrogen–oxygen
ionic nitrate $(NO_3)^-$
covalent nitrate $R—O—NO_2$
nitro $R—NO_2$ unconj.
nitro conj.
covalent nitrate R—O—NO
nitroso R—NO
ammonium NH_4^+
S
M
ASSIGNMENTS
OH and NH str.
CH str.
—C≡X str.
C=O str.
C=N str.
C=C str.
NH bend
CH bend
OH bend
C—O str.
C—N str.
C—C str.
CH rock
NH rock
N. B. COLTHUP
4000 cm^{-1} 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400
2.50 μm 2.75 3.00 3.25 3.50 3.75 4.00 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 9.0 10 11 12 13 14 15 20 25

Answers to Selected Problems

CHAPTER 1

1-1. 8 + 8, 8 + 9, 8 + 10
1-2. a. 3 **b.** 5 **c.** 6 **d.** 7
1-3. 7
1-4. a. C 2 and 4; Si 10 and 4 **b.** O 2 and 6; S 10 and 6 **c.** N 2 and 5; P 10 and 5
1-5. a. 1 **b.** 4*s*
1-6. a. Cl—CH_3 **b.** H—OH **c.** H—F **d.** Cl—CH_3
1-7. a. KCl **b.** Cl_2
1-9. a. $\overset{\delta-}{HO}—\overset{\delta+}{H}$ **c.** $\overset{\delta+}{H_3C}—\overset{\delta-}{NH_2}$ **e.** $\overset{\delta-}{HO}—\overset{\delta+}{Br}$ **g.** $\overset{\delta+}{I}—\overset{\delta-}{Cl}$
b. $\overset{\delta-}{F}—\overset{\delta+}{Br}$ **d.** $\overset{\delta+}{H_3C}—\overset{\delta-}{Cl}$ **f.** $\overset{\delta-}{H_3C}—\overset{\delta+}{Li}$ **h.** $\overset{\delta+}{H_2N}—\overset{\delta-}{OH}$
1-10. a. LiH and HF **b.** Its hydrogen has the greatest electron density.
1-11. a. oxygen **b.** oxygen **c.** oxygen **d.** hydrogen
1-14. a. CH_3CH_2OH CH_3OCH_3
b. $CH_3CH_2CH_2OH$ $CH_3CH(OH)CH_3$ $CH_3CH_2OCH_3$
1-15. a. $CH_3CH_2\ddot{N}H_2$ **c.** $CH_3CH_2\ddot{O}H$ (with lone pairs) **e.** $CH_3CH_2\ddot{Cl}:$ (with lone pairs)
b. $CH_3\ddot{N}HCH_3$ **d.** $CH_3\ddot{O}CH_3$ (with lone pairs) **f.** $H\ddot{O}\ddot{N}H_2$ (with lone pairs)
1-16. a. $CH_3CH_2CH_2Cl$ **c.** $CH_3CH_2C(=O)N(CH_3)CH_2CH_3$
b. $CH_3C(=O)OCH_2CH_3$ **d.** $CH_3CH_2C{\equiv}N$
1-17. a. Cl **b.** O **c.** N **d.** C and H
1-19. The C—C bonds are formed by sp^3–sp^3 overlap; the C—H bonds are formed by sp^3–s overlap.
1-23. a. 120° **b.** 120° **c.** 107.3°
1-24. the nitrogen
1-25. most = water; least = methane
1-27. a. relative lengths: $Br_2 > Cl_2$; relative strengths: $Cl_2 > Br_2$
b. relative lengths; $CH_3Br > CH_3Cl > CH_3F$; relative strengths: $CH_3F > CH_3Cl > CH_3Br$
1-28. a. 1. C–I **2.** C–Cl **3.** H–Cl **b. 1.** C–Cl **2.** C–C **3.** H–F
1-30. σ
1-33. a. 109.5° **b.** 107.3° **c.** 109.5° **d.** 109.5°
1-36. a and d

CHAPTER 2

2-1. CO_2 and CCl_4
2-2. a. $Cl^- + {}^+NH_4$ **b.** $HO^- + NH_3$
2-3. a. 1. ${}^+NH_4$ **2.** HCl **3.** H_2O **4.** H_3O^+ **b. 1.** ${}^-NH_2$ **2.** Br^- **3.** NO_3^- **4.** HO^-
2-4. a. 5.2 **b.** 3.4×10^{-3}
2-5. weaker
2-7. a. basic **b.** acidic **c.** basic
2-8. a. $CH_3CH_2\overset{+}{O}H_2$ **c.** $CH_3C(=O)OH$ **e.** $CH_3CH_2C(={}^+OH)OH$
b. CH_3CH_2OH **d.** $CH_3CH_2\overset{+}{N}H_3$
2-10. 40, 15, 5, 10
2-11. a. CH_3COO^- **b.** ${}^-NH_2$ **c.** H_2O
2-12. $CH_3NH^- > CH_3O^- > CH_3NH_2 > CH_3C(=O)O^- > CH_3OH$
2-13. acid
2-16. HO^-, CH_3NH_2, $HC{\equiv}C^-$
2-17. ${}^-CH_3 > {}^-NH_2 > HO^- > F^-$
2-18. $CH_3CH_2^- > H_2C{=}CH^- > HC{\equiv}C^-$
2-19. the one on the right
2-21. $F^- > Cl^- > Br^- > I^-$
2-22. a. oxygen **b.** H_2S **c.** CH_3SH
2-23. a. HBr **b.** $CH_3CH_2CH_2\overset{+}{O}H_2$ **c.** the one on the right **d.** $CH_3CH_2CH_2SH$
2-24. a. I^- **b.** F^- **c.** F^-
2-25. a. HO^- **b.** NH_3 **c.** CH_3O^- **d.** CH_3O^-
2-26. a. $CH_3OCH_2CH_2OH$ **b.** $CH_3CH_2CH_2\overset{+}{O}H_2$
c. $CH_3CH_2OCH_2CH_2OH$ **d.** $CH_3CH_2C(=O)OH$
2-27. a. $CH_3CH(F)C(=O)O^-$ **b.** $CH_3CH_2CH(Cl)C(=O)O^-$ **c.** $BrCH_2CH_2C(=O)O^-$ **d.** $CH_3CH_2C(=O)CH_2O^-$
2-30. $CH_3S(=O)_2—OH$ forms a more stable base because the electrons left behind when the proton is removed are shared by 3 oxygens.
2-31. a. CH_3COO^- **b.** $CH_3CH_2\overset{+}{N}H_3$ **c.** H_2O **d.** Br^-
e. ${}^+NH_4$ **f.** ${}^-C{\equiv}N$ **g.** NO_2^- **h.** NO_3^-
2-32. a. 1. neutral **2.** neutral **3.** charged **4.** charged **5.** charged **6.** charged
b. 1. charged **2.** charged **3.** charged **4.** charged **5.** neutral **6.** neutral
c. 1. neutral **2.** neutral **3.** neutral **4.** neutral **5.** neutral **6.** neutral
2-34. b. >12.7 **c.** ≤ 2.8
2-35. a. $CH_3COO^- + H^+ \rightleftharpoons CH_3COOH$
b. $CH_3COOH + HO^- \rightleftharpoons CH_3COO^- + H_2O$
2-37. a. $CH_3O^- + H_2O$ **b.** $NH_3 + H_2O$ **c.** $CH_3NH_2 + H_2O$ **d.** $CH_3COO^- + H_2O$

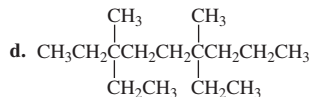
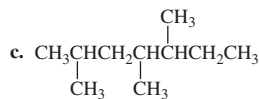
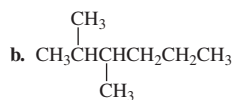
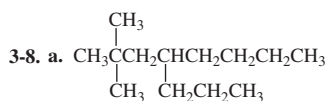
CHAPTER 3

3-1. a. 36 hydrogens **b.** 36 carbons
3-3. a. *n*-propyl alcohol or propyl alcohol **b.** butyl methyl ether
c. *n*-propylamine or propylamine
3-4.
$CH_3CH_2CH_2CH_2Br$ — **butyl bromide or *n*-butyl bromide**
$CH_3CH(CH_3)CH_2Br$ — **isobutyl bromide**
$CH_3CH_2CH(Br)CH_3$ — ***sec*-butyl bromide**
$CH_3C(CH_3)_2Br$ — ***tert*-butyl bromide**
3-5. a. $CH_3CH(CH_3)OH$ **b.** $CH_3CH(CH_3)CH_2CH_2F$ **c.** $CH_3CH_2CH(CH_3)I$
d. $CH_3C(CH_3)(OH)CH_2CH_3$ **e.** $CH_3C(CH_3)_2NH_2$ **f.** $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2Br$
3-6. a. ethyl methyl ether **b.** ethylpropylamine **c.** *sec*-butylamine
d. *n*-butyl alcohol or butyl alcohol **e.** isobutyl bromide
f. *sec*-butyl chloride
3-7. a. $CH_3CH(CH_3)CH_2CH_3$ **2-methylbutane** **b.** $CH_3C(CH_3)_2CH_3$ **2,2-dimethylpropane**

CH_3
3-8. a. $CH_3CCH_2CHCH_2CH_2CH_2CH_3$
CH_3 $CH_2CH_2CH_3$

CH_3
b. $CH_3CHCHCH_2CH_2CH_3$
CH_3

CH_3
c. $CH_3CHCH_2CHCHCH_2CH_3$
CH_3 CH_3

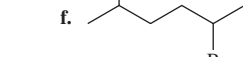
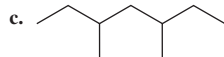
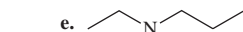
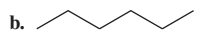
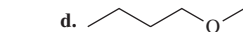
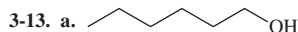
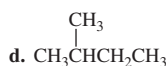
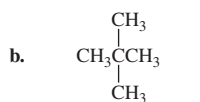
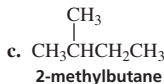
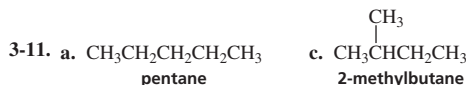
CH_3 CH_3
d. $CH_3CH_2CCH_2CH_2CCH_2CH_2CH_3$
CH_2CH_3 CH_2CH_3

3-10. a. 2,2,4-trimethylhexane **b.** 2,2-dimethylbutane **c.** 2,2,5-trimethylhexane **d.** 5-ethyl-4,4-dimethyloctane **e.** 3,3-diethylhexane **f.** 2,5-dimethylheptane

3-11. a. $CH_3CH_2CH_2CH_2CH_3$ **pentane**

c. $CH_3CHCH_2CH_3$ (with CH_3 on C2) **2-methylbutane**

b. CH_3CCH_3 (with CH_3 above and below) **2,2-dimethylpropane**

d. $CH_3CHCH_2CH_3$ (with CH_3 on C2) **2-methylbutane**

3-13. a. OH **b.** **c.** **d.** O **e.** N H **f.** Br

3-14. a. $C_{10}H_{20}O$ **b.** $C_{10}H_{20}O_2$

3-16. a. 1-ethyl-2-methylcyclopentane **b.** ethylcyclobutane **c.** 1-ethyl-3-methylcyclohexane **d.** 3,6-dimethyldecane **e.** heptane **f.** 1-bromohexane

3-17. a. same **b.** same

3-18. a. *sec*-butyl chloride, 2-chlorobutane **b.** cyclohexyl bromide, bromocyclohexane **c.** isohexyl chloride, 1-chloro-4-methylpentane **d.** isopropyl fluoride, 2-fluoropropane

3-19. a. tertiary **b.** tertiary **c.** primary

3-20. a. methylpropylamine, secondary **b.** trimethylamine, tertiary **c.** diethylamine, secondary **d.** butyldimethylamine, tertiary

3-22. a. 104.5° **b.** 107.3° **c.** 104.5°

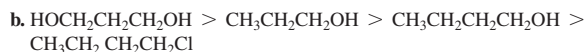
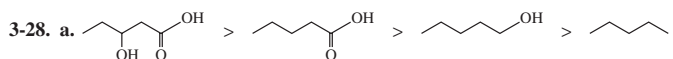
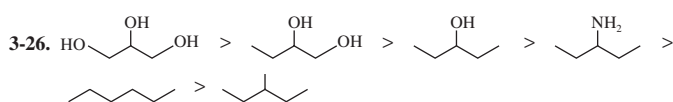
3-23. pentane

3-24. a. O–H covalent bond **b.** O–H covalent bond

3-25. a. 1, 4, 5 **b.** 1, 2, 4, 5, 6

3-26. HO OH OH > OH OH > OH > NH_2 > >

3-28. a. OH OH O > OH O > OH >

b. $HOCH_2CH_2CH_2OH > CH_3CH_2CH_2OH > CH_3CH_2CH_2CH_2OH >$ $CH_3CH_2\ CH_2CH_2Cl$

3-29. ethanol

3-30. hexethal

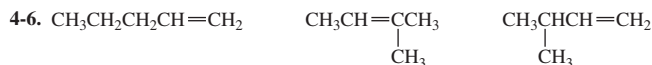
3-35. isopropylhexane

3-36. a. cis **b.** trans **c.** cis **d.** trans

CHAPTER 4

4-1. a. $CH_3CH_2CH_2OH$ CH_3CHOH (with CH_3 below) $CH_3CH_2OCH_3$ **b.** 7

4-3. a. 5 **b.** 4 **c.** 4 **d.** 6

4-6. $CH_3CH_2CH_2CH{=}CH_2$ $CH_3CH{=}CCH_3$ (with CH_3 below) $CH_3CHCH{=}CH_2$ (with CH_3 below)

4-7. a. —I > —Br > —OH > —CH_3
b. —OH > —CH_2Cl > —$CH{=}CH_2$ > —CH_2CH_2OH

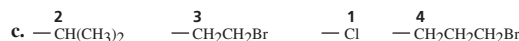
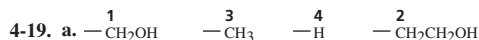
4-8. *Z*

4-11. a. (*E*)-2-heptene **b.** (*Z*)-3,4-dimethyl-2-pentene **c.** (*Z*)-1-chloro-3-ethyl-4-methyl-3-hexene

4-13. b and d

4-14. a, c, and f

4-16. a, c, and f

4-19. a. 1 —CH_2OH 3 —CH_3 4 —H 2 —CH_2CH_2OH
b. 2 —$CH{=}O$ 1 —OH 4 —CH_3 3 —CH_2OH
c. 2 —$CH(CH_3)_2$ 3 —CH_2CH_2Br 1 —Cl 4 —$CH_2CH_2CH_2Br$

4-20. a. (*R*)-2-bromobutane **b.** (*R*)-1,3-dichlorobutane

4-21. a. *R* **b.** *R* **c.** *R* **d.** *R*

4-22. a. identical **b.** enantiomers **c.** enantiomers

4-23. a. 0 **b.** +79. **c.** −79

4-24. a. levorotatory **b.** dextrorotatory

4-27. a. *S* **b.** *R* **c.** *R* **d.** *S*

4-28. +6.7

4-29. a. −24 **b.** 0

4-30. do not know

4-31. a. enantiomers **b.** identical **c.** diastereomers

4-32. a. 8 **b.** $2^8 = 256$

4-34. A, C, E

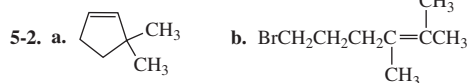
4-35. a. diastereomers **b.** enantiomers **c.** identical **d.** constitutional isomers

4-38. A = identical, B = enantiomer, C = diastereomer, D = identical

4-39. B, D, and F

4-42. the one on the left

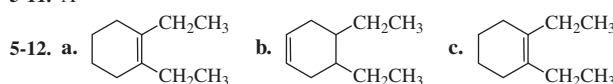
CHAPTER 5

5-1. a. 2 **b.** 4

5-2. a. CH_3 CH_3 **b.** $BrCH_2CH_2CH_2C{=}CCH_3$ (with CH_3 on each alkene carbon)
c. $CH_3CH_2OCH{=}CH_2$ **d.** $CH_2{=}CHCH_2OH$

5-3. a. 4-methyl-2-pentene **b.** 2-chloro-3,4-dimethyl-3-hexene **c.** 1-bromocyclopentene **d.** 1,5-dimethylcyclohexene **e.** 1-bromo-4-methyl-3-hexene **f.** 1-bromo-2-methyl-1,3-pentadiene

5-4. electrophiles: $CH_3\overset{+}{C}HCH_3$; nucleophiles: H^-, CH_3O^-, $CH_3C{\equiv}CH$, NH_3

5-11. A

5-12. a. CH_2CH_3 CH_2CH_3 **b.** CH_2CH_3 CH_2CH_3 **c.** CH_2CH_3 CH_2CH_3

5-13. *cis*-3,4-dimethyl-3-hexene > *trans*-3-hexene > *cis*-3-hexene > *cis*-2,5-dimethyl-3-hexene

5-14. decreasing; increasing

5-15. a. a and b **b.** b **c.** c

5-18. a. first step **b.** revert to reactants **c.** second step

5-19. a. 1 **b.** 2 **c.** C → D **d.** C → B **e.** C → D **f.** B → C **g.** C → B

5-20. $\Delta G^{\ddagger}$

CHAPTER 6

6-2. a. 0 **b.** ethyl cation because of hyperconjugation

6-3. a. 1. 3 **2.** 3 **3.** 6 **b.** *sec*-butyl cation

6-4. a. $CH_3CH_2\overset{+}{C}CH_3$ (with CH_3 above) > $CH_3CH_2\overset{+}{C}HCH_3$ > $CH_3CH_2CH_2\overset{+}{C}H_2$
b. $CH_3CHCH_2\overset{+}{C}H_2$ (with CH_3 below) > $CH_3CHCH_2\overset{+}{C}H_2$ (with Cl below) > $CH_3CHCH_2\overset{+}{C}H_2$ (with F below)

6-5. a. $CH_3CH_2C{=}CH_2$ (with CH_3 above) **b.** CH_2

6-6. **a.** $CH_3CH_2CHCH_3$ (Br on C-2) **c.** (1-bromo-1-methylcyclopentane: CH_3, Br) **e.** (1-bromo-1-methylcyclohexane: CH_3, Br)

b. $CH_3CH_2CCH_3$ (CH_3, Br on C-2) **d.** $CH_3CCH_2CH_2CH_3$ (CH_3, Br on C-2) **f.** $CH_3CH_2CHCH_3$ (Br)

6-7. **a.** $CH_2{=}CCH_3$ (CH_3) **b.** cyclohexyl$-CH_2CH{=}CH_2$

c. cyclohexyl$-C{=}CH_2$ (CH_3) **d.** cyclohexylidene$=CHCH_3$ or cyclohexenyl$-CH_2CH_3$

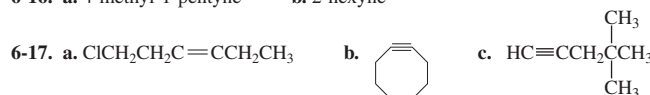
6-9. **a.** 3 **b.** 2 **c.** first step

6-10. **a.** $CH_3CH_2CH_2CHCH_3$ (OH) **c.** $CH_3CH_2CH_2CHCH_2CH_3$ (OH) and $CH_3CH_2CH_2CH_2CHCH_3$ (OH) **d.** (1-methylcyclohexanol: CH_3, OH)

b. cyclohexyl$-OH$

6-15. **a.** (*R*)-malate and (*S*)-malate **b.** (*R*)-malate and (*S*)-malate

6-16. **a.** 4-methyl-1-pentyne **b.** 2-hexyne

6-17. **a.** $ClCH_2CH_2C{\equiv}CCH_2CH_3$ **b.** (cyclooctyne) **c.** $HC{\equiv}CCH_2CCH_3$ (CH_3, CH_3)

6-19. **a.** 5-bromo-2-pentyne **b.** 6-bromo-2-chloro-4-octyne **c.** 3-ethyl-1-hexyne

6-20. **a.** 6-methyl-2-octyne **b.** 5-ethyl-4-methyl-1-heptyne **c.** 2-bromo-4-octyne

6-21. **a.** sp^2–sp^2 **b.** sp^2–sp^3 **c.** sp–sp^2 **d.** sp–sp^3 **e.** sp–sp **f.** sp^2–sp^2 **g.** sp^2–sp^3 **h.** sp–sp^3 **i.** sp^2–sp

6-22. **a.** $CH_2{=}CCH_3$ (Br) **b.** CH_3CCH_3 (Br, Br) **c.** $CH_3CH_2CCH_3$ (Br, Br)

d. $CH_3CCH_2CH_2CH_3$ (Br, Br) + $CH_3CH_2CCH_2CH_3$ (Br, Br)

6-23. $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_3$ and $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$

6-24. **a.** $CH_3C{=}CH$ **b.** $CH_3CH_2C{=}CCH_2CH_3$ **c.** $HC{\equiv}C-$cyclohexyl

6-25. $CH_3CH{=}CCH_2CH_2CHCH_3$ (OH; CH_3) and $CH_3CH_2CH{=}CHCH_2CHCH_3$ (OH; CH_3)

6-26. **a.** $CH_2{=}CCH_3$ (OH)

b. $CH_3CH{=}CCH_2CH_2CH_3$ (OH) and $CH_3CH_2C{=}CHCH_2CH_3$ (OH)

c. $CH_2{=}C-$cyclohexyl (OH) and $CH_3C{=}$cyclohexylidene (OH)

6-27. **a.** $CH_3CH_2CH_2C{\equiv}CH$ or $CH_3CH_2C{\equiv}CCH_3$ $\xrightarrow[\text{Pd/C}]{H_2}$

b. $CH_3C{\equiv}CCH_3$ $\xrightarrow[\text{Lindlar catalyst}]{H_2}$

c. $CH_3CH_2CH_2CH_2C{\equiv}CH$ $\xrightarrow[\text{Lindlar catalyst}]{H_2}$

CHAPTER 7

7-4. **a.** all are the same length **b.** 2/3 of a negative charge

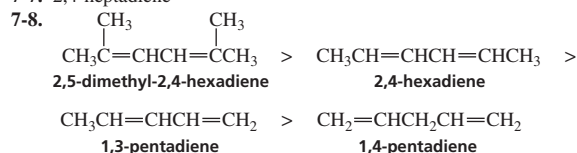
7-5. the dianion > the monoanion > the neutral compound

7-6. acetate ion

7-7. 2,4-heptadiene

7-8. $CH_3C{=}CHCH{=}CCH_3$ (CH_3, CH_3) > $CH_3CH{=}CHCH{=}CHCH_3$ >
2,5-dimethyl-2,4-hexadiene **2,4-hexadiene**

$CH_3CH{=}CHCH{=}CH_2$ > $CH_2{=}CHCH_2CH{=}CH_2$
1,3-pentadiene **1,4-pentadiene**

7-9. **a.** (cyclohexenyl$-\overset{+}{C}HCH_3$) **b.** (phenyl$-\overset{+}{C}(CH_3)_2$)

7-10. **a.** the one on the left **b.** the one on the right

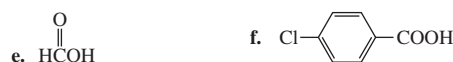
7-11. **a.** the one on the right **b.** the one on the left **c.** the one on the right

7-12. **a.** ethylamine **b.** ethoxide ion **c.** ethoxide ion

7-13. **a.** donates electrons by resonance and withdraws electrons inductively
b. donates electrons by hyperconjugation
c. withdraws electrons by resonance and withdraws electrons inductively
d. donates electrons by resonance and withdraws electrons inductively
e. donates electrons by resonance and withdraws electrons inductively
f. withdraws electrons inductively

7-14. **a.** $ClCH_2\overset{O}{\overset{\|}{C}}OH$ **b.** $O_2NCH_2\overset{O}{\overset{\|}{C}}OH$

c. (p-acetylbenzoic acid: COOH, $CH_3C{=}O$) **d.** $H_3\overset{+}{N}CH_2\overset{O}{\overset{\|}{C}}OH$

e. $H\overset{O}{\overset{\|}{C}}OH$ **f.** $Cl-C_6H_4-COOH$

7-18. **a.** 6-bromo-6-methyl-1-heptene **b.** 5-chloro-5-methylcycloheptene

7-19. **a.** $CH_3CHCHCH{=}CHCH_3$ (Cl Cl) + $CH_3CHCH{=}CHCHCH_3$ (Cl, Cl)

b. $CH_3CH_2C-C{=}CHCH_3$ (Br; CH_3CH_3) + $CH_3CH_2C{=}CCHCH_3$ (Br; CH_3CH_3)

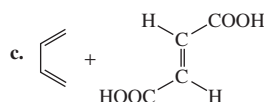
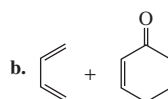
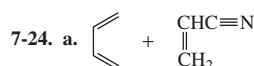
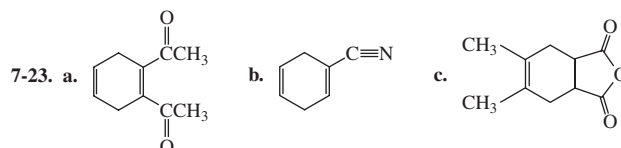
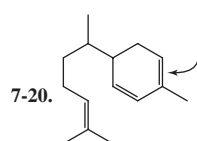
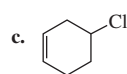
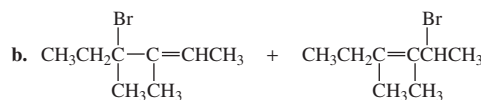
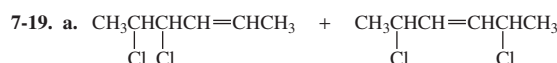
c. (3-chlorocyclohexene: Cl)

7-20. (structure)

7-23. **a.** (cyclohexadiene with two $\overset{O}{\overset{\|}{C}}CH_3$ groups) **b.** (cyclohexenyl$-C{\equiv}N$) **c.** (bicyclic anhydride with CH_3, CH_3; O)

7-24. **a.** (butadiene) + $\underset{CH_2}{\overset{CHC\equiv N}{\|}}$

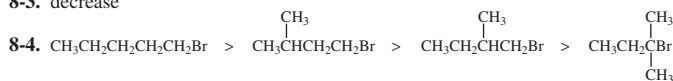
b. (butadiene) + (cyclohexenone: O)

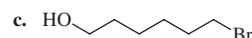
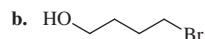
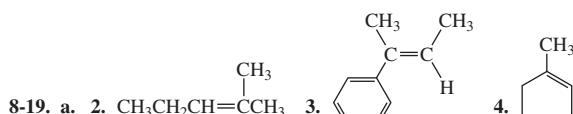
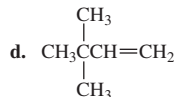
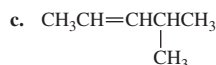
c. (butadiene) + $\overset{H}{}C{=}C$ (H, COOH; HOOC, H)

7-25. cycloheptatrienyl cation

7-27. C

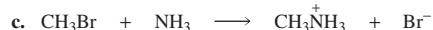
CHAPTER 8

8-2. **a.** tripled **b.** half as fast.
8-3. decrease

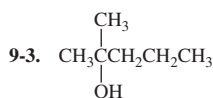
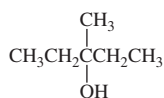
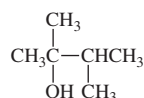
8-4. $CH_3CH_2CH_2CH_2CH_2Br$ > $CH_3CH(CH_3)CH_2CH_2Br$ > $CH_3CH_2CH(CH_3)CH_2Br$ > $CH_3CH_2C(CH_3)_2Br$

8-5. **a.** 2-methoxybutane **b.** (*S*)-2-methoxybutane **c.** (*R*)-3-hexanol **d.** 3-pentanol
8-7. **a.** 1-bromo-2-methylbutane **b.** 2-bromopropane **c.** 2-bromobutane **d.** 1-bromo-2-phenylethane
8-8. **a.** $CH_3CH_2Br + HO^-$ **b.** $CH_3CH_2Cl + CH_3O^-$
8-11. **a.** $CH_3CH_2OCH_2CH_2CH_3$ **b.** $CH_3CH_2C{\equiv}CCH_3$ **c.** $CH_3CH_2\overset{+}{N}(CH_3)_3Br^-$ **d.** $CH_3CH_2SCH_2CH_3$
8-12. **a.** (*R*)-3-methoxy-3-methylhexane + (*S*)-3-methoxy-3-methylhexane **b.** 3-methoxy-3-methylpentane
8-13. 2-iodo-2-methylpentane > 2-bromo-2-methylpentane > 2-chloro-2-methylpentane > 3-chloropentane
8-15. a and b

8-16. **a.** HO(CH₂)₆Br (skeletal) **b.** HO(CH₂)₅Br (skeletal) **c.** HO(CH₂)₇Br (skeletal)

8-18. **a.** $CH_3CH_2CH_2CH{=}CHCH_3$ **b.** $CH_3CH_2CH{=}C(CH_3)CH_3$ **c.** $CH_3CH{=}CHCH(CH_3)CH_3$ **d.** $CH_3C(CH_3)_2CH{=}CH_2$

8-19. **a.** **2.** $CH_3CH_2CH{=}C(CH_3)CH_3$ **3.** $C_6H_5C(CH_3){=}C(CH_3)H$ **4.** 1-methylcyclohexene
b. the same as in an E2

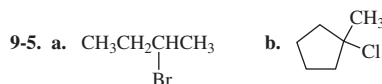
8-20. **a.** *tert*-butyl bromide **b.** *tert*-butyl bromide
8-21. **a.** B **b.** B **c.** B **d.** A
8-23. **a.** 1-bromopropane **b.** 1-iodo-1-methylcyclohexane **c.** 2-bromo-2-methylbutane
8-24. **a.** primarily substitution **b.** substitution and elimination **c.** substitution and elimination **e.** only elimination
8-25. it would increase
8-26. **a.** decrease **b.** decrease **c.** increase

8-27.
a. $CH_3Br + HO^- \longrightarrow CH_3OH + Br^-$
b. $CH_3I + HO^- \longrightarrow CH_3OH + I^-$
c. $CH_3Br + NH_3 \longrightarrow CH_3\overset{+}{N}H_3 + Br^-$
d. $CH_3Br + HO^- \xrightarrow{\text{DMSO}} CH_3OH + Br^-$
e. $CH_3Br + NH_3 \xrightarrow{\text{EtOH}} CH_3\overset{+}{N}H_3 + Br^-$

8-29. **a.** 50% water/50% ethanol **b.** *tert*-butyl alcohol, *tert*-butyl ethyl ether, and 2-methylpropene in 50% water/50% ethanol; *tert*-butyl ethyl ether and 2-methylpropene in ethanol.

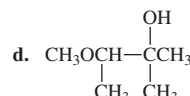
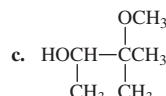
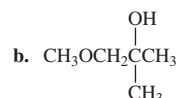
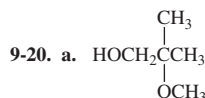
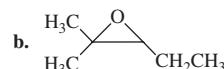
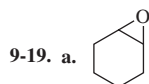
CHAPTER 9

9-2. **a.** 1-pentanol **b.** 4-methylcyclohexanol **c.** 5-methyl-2-hexanol **d.** 3-ethyl-1-hexanol **e.** 5-chloro-2-methyl-2-pentanol **f.** 2,6-dimethyl-4-octanol

9-3. $CH_3C(CH_3)(OH)CH_2CH_2CH_3$ **2-methyl-2-pentanol**; $CH_3CH_2C(CH_3)(OH)CH_2CH_3$ **3-methyl-3-pentanol**; $CH_3C(CH_3)(OH){-}CH(CH_3)CH_3$ **2,3-dimethyl-2-butanol**

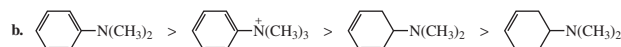
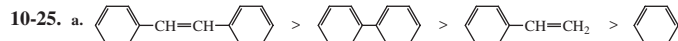
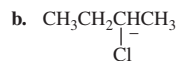
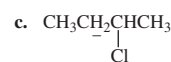
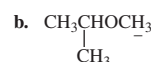
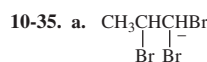
9-4. no lone pair

9-5. **a.** $CH_3CH_2CH(Br)CH_3$ **b.** 1-chloro-1-methylcyclopentane

9-8. 3° > 1° > 2°
9-9. B
9-12. (*E*)-3,4-dimethyl-3-hexene (major) + (*Z*)-3,4-dimethyl-3-hexene
9-13. **a.** 3-ethyl-2,4-dimethyl-3-hexene **b.** (*E*)-3-ethyl-2,4-dimethyl-3-hexene
9-14. **a.** 3-pentanone **a.** no reaction **a.** 1-pentanal
9-15. **a.** 2-butanol **b.** benzyl alcohol **c.** 1-butanol
9-16. **a.** **1.** methoxyethane **2.** ethoxyethane **3.** 4-methoxyoctane **4.** 1-propoxybutane **b.** no **c.** **1.** ethyl methyl ether **2.** diethyl ether **3.** none **4.** butyl propyl ether

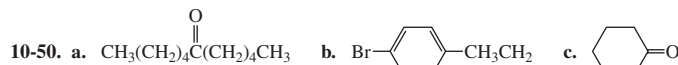
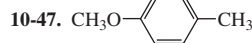
9-19. **a.** cyclohexene oxide (epoxide) **b.** epoxide with H_3C, H_3C on one carbon and CH_2CH_3 on the other

9-20. **a.** $HOCH_2C(CH_3)(OCH_3)CH_3$ **b.** $CH_3OCH_2C(OH)(CH_3)CH_3$ **c.** $HOCH(CH_3){-}C(OCH_3)(CH_3)CH_3$ **d.** $CH_3OCH(CH_3){-}C(OH)(CH_3)CH_3$

9-21. noncyclic ether
9-24. the one on the right
9-25. The first one is too insoluble; the second is too reactive; the third is too unreactive.

CHAPTER 10

10-1. B, C, E
10-3. $m/z = 57$
10-5. **a.** C_5H_{12} **b.** $C_6H_{12}O$ **c.** $C_5H_{10}O_2$ **d.** $C_6H_{12}NO$
10-6. C_6H_{14}, $C_5H_{10}O$, $C_4H_6O_2$
10-7. 2,6-dimethylheptane
10-8. 1-bromopropane
10-10. C_6H_{14}
10-11. **a.** yes **b.** no
10-14. **a.** IR **b.** UV
10-15. **a.** 2000 cm^{-1} **b.** 8 μm
10-16. **a.** C≡C **b.** C—H stretch **c.** C═N **d.** C═O
10-17. **a.** carbon–oxygen stretch of a phenol **b.** carbon–oxygen double-bond stretch of a ketone **c.** C—N stretch of aniline
10-18. sp^3
10-19. C—O bond of pentanoic acid has partial double bond character
10-20. ethanol dissolved in carbon disulfide
10-21. tertiary amine
10-24. methyl vinyl ketone
10-25. **a.** $C_6H_5CH{=}CHC_6H_5$ > biphenyl > $C_6H_5CH{=}CH_2$ > benzene
b. $C_6H_5N(CH_3)_2$ > $C_6H_5\overset{+}{N}(CH_3)_3$ > cyclohexenyl-$N(CH_3)_2$ > cyclohexyl-$N(CH_3)_2$
10-26. **a.** left = purple; right = blue **b.** They would be the same color.
10-27. yellow and blue
10-28. monitor increase in absorption at 340 nm
10-29. 5.0
10-31. **a.** 2 **b.** 1 **c.** 1 **d.** 3 **e.** 3 **f.** 3
10-33. to the right of the TMS signal
10-34. **a.** in each structure, it is the proton(s) on the carbon on the right-hand side of the structure **b.** in each structure, it is the protons on the methyl group on the left-hand side of the structure
10-35. **a.** $CH_3CH(Br)CHBr$ **b.** $CH_3CH(CH_3)OCH_3$ **c.** $CH_3CH_2CH(Cl)CH_3$
10-36. **a.** $CH_3CH_2CH_2Cl$ **b.** $CH_3CH_2CH(Cl)CH_3$

10-38. The compounds have different integration ratios: 2:9, 1:3, and 2:1
10-39. B
10-40. first spectrum = 1-iodopropane
10-42. **a.** 2-chloropropanoic acid **b.** 3-chloropropanoic acid

10-47. CH_3O–(benzene ring)–CH_3

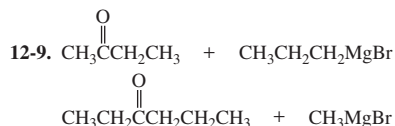
10-50. **a.** $CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}(CH_2)_4CH_3$ **b.** Br–(benzene ring)–CH_3CH_2 **c.** (cyclohexane ring)=O

CHAPTER 11

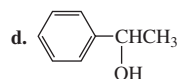
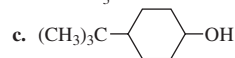
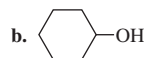
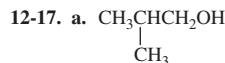
11-1. **a.** benzyl acetate **b.** isopentyl acetate **c.** methyl butyrate
11-2. **a.** potassium butanoate, potassium butyrate **b.** isobutyl butanoate, isobutyl butyrate **c.** pentanoyl chloride, valeryl chloride **d.** 5-methylhexanoic acid, methylcaproic acid **e.** propanamide, propionamide **f.** *N,N*-dimethylhexanamide, *N,N*-dimethylcaproamide
11-4. B
11-5. In an alcohol because there is no electron delocalization.
11-6. **a.** sodium acetate **b.** no reaction
11-7. **a.** new **b.** no reaction **c.** mixture of two
11-8. **a.** no reaction **b.** sodium acetate **c.** no reaction **d.** no reaction
11-16. **a.** isopropyl butyrate **b.** ethyl acetate
11-18. **a.** propoxide ion **b.** H^+ would destroy the nucleophilicity of the amine; HO^- and RO^- would provide the wrong nucleophile
11-20. **a.** butyrate ion and iodomethane **b.** acetate ion and 1-iodooctane
11-21. 2 and 5
11-23. B > C > A
11-24. **a.** butanenitrile, propyl cyanide **b.** 4-methylpentanenitrile, isopentyl cyanide
11-25. **a.** 1-bromopropane **b.** 1-bromo-2-methylpropane **c.** 1-bromopentane
11-28. **a.** acetyl chloride and butyrate ion **b.** butyryl chloride and acetate ion
11-29. **a.** butanoyl chloride and ethylamine **b.** ethanoyl chloride and dimethylamine
11-30. **a.** propanoic acid + phosphorus trichloride followed by phenol
b. acetic acid + phosphorus trichloride followed by ethylamine
c. propanoic acid + phosphorus trichloride followed by acetate ion

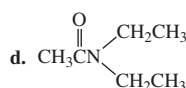
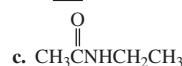
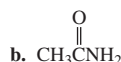
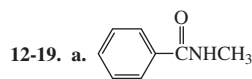
CHAPTER 12

12-3. **a.** 4-heptanone, dipropyl ketone **b.** 2-methyl-4-heptanone, isobutyl propyl ketone **c.** 4-ethylhexanal, γ-ethylcaproaldehyde
12-4. if elsewhere would not be a ketone
12-5. **a.** 2-heptanone **b.** chloromethyl phenyl ketone
12-6. **a.** ethane + hydroxide ion **b.** ethane + methoxide ion **c.** ethane + $CH_3\overset{-}{N}H$ **d.** ethane + acetylide ion
12-7. C
12-8. **a.** 2-butanol **b.** 2-methyl-2-pentanol **c.** 1-methylcyclohexanol

12-9. $CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3$ + $CH_3CH_2CH_2MgBr$

$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$ + CH_3MgBr

12-10. **a.** two; (*R*)-3-methyl-3-hexanol and (*S*)-3-methyl-3-hexanol
b. one; 2-methyl-2-pentanol
12-14. B and D

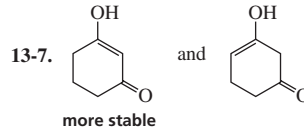
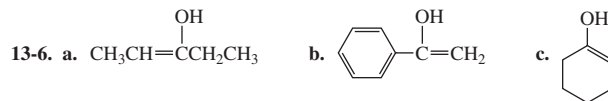
12-17. **a.** $CH_3\underset{CH_3}{\underset{|}{C}}HCH_2OH$ **b.** (cyclohexane ring)–OH
c. $(CH_3)_3C$–(cyclohexane ring)–OH **d.** (benzene ring)–$\underset{OH}{\underset{|}{C}}HCH_3$

12-18. **a.** 1-butanol and ethanol **b.** benzyl alcohol + methanol. **c.** 1-pentanol

12-19. **a.** (benzene ring)–$\overset{O}{\overset{\|}{C}}NHCH_3$ **b.** $CH_3\overset{O}{\overset{\|}{C}}NH_2$
c. $CH_3\overset{O}{\overset{\|}{C}}NHCH_2CH_3$ **d.** $CH_3\overset{O}{\overset{\|}{C}}N(CH_2CH_3)_2$

12-23. **a.** 1, 5, 6 **b.** 2, 3, 4

CHAPTER 13

13-2. **a.** the one on the left **b.** the one on the right
13-3. no competition for electron delocalization onto oxygen
13-4. The proton on the nitrogen is more acidic than the proton on the α-carbon.
13-5. HO^- will react with the acyl chloride to form a carboxylate ion.

13-6. **a.** $CH_3CH{=}\overset{OH}{\overset{|}{C}}CH_2CH_3$ **b.** (benzene ring)–$\overset{OH}{\overset{|}{C}}{=}CH_2$ **c.** (cyclohexene ring with OH on double-bond carbon)

13-7. (cyclohexenone enol: OH on C=C conjugated with C=O) and (cyclohexenone enol: OH on C=C not conjugated with C=O)
more stable

13-13. **a.** butanal **b.** 3-pentanone

13-17. **a.** $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}\underset{CH_2CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OCH_3$ **b.** $CH_3\underset{CH_3}{\underset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}\underset{CHCH_3 \atop CH_3}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OCH_2CH_3$

13-18. A, B, and D
13-20. A and D
13-23. **a.** 3 **b.** 7

CHAPTER 14

14-3. 6
14-4. the one on the third carbon from the left
14-5. **a.** 3 **b.** 1 **c.** 3 **d.** 5 **e.** 5 **f.** 4
14-7. chlorination
14-9. 5
14-10. **a.** D **b.** B
14-11. 4

CHAPTER 15

15-1. **a.** $CH_2{=}CHCl$ **b.** $CH_2{=}\underset{\overset{|}{C}OCH_3 \atop \|\,O}{C}CH_3$ **c.** $CF_2{=}CF_2$

15-4. beach balls
15-5. **a.** $CH_2{=}CH$–(benzene ring)–OCH_3 > $CH_2{=}CH$–(benzene ring)–CH_3 > $CH_2{=}CH$–(benzene ring)–NO_2

b. $CH_2{=}CHOCH_3$ > $CH_2{=}CHCH_3$ > $CH_2{=}CH\overset{O}{\overset{\|}{C}}OCH_3$

15-6. **a.** $CH_2{=}CH$–(benzene ring)–NO_2 > $CH_2{=}CH$–(benzene ring)–CH_3 > $CH_2{=}CH$–(benzene ring)–OCH_3

b. $CH_2{=}CHC{\equiv}N$ < $CH_2{=}CHCl$ < $CH_2{=}CHCH_3$

15-8. The carbocation would be unstable because of the electron withdrawing ester group.

15-9. **a.** $CH_2{=}\underset{CH_3}{\underset{|}{C}}CH_3$ + BF_3 + H_2O

b. $CH_2{=}CH$–N(pyrrolidinone ring, C=O) + BF_3 + H_2O **c.** $CH_2{=}\underset{\overset{|}{C}OCH_3 \atop \|\,O}{C}H$ + BuLi

15-15. a. $-NHCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}-$

b. $-NH(CH_2)_4NH\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}NH(CH_2)_4NH\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}-$

CHAPTER 16

16-1. D-Ribose is an aldopentose. D-Sedoheptulose is a ketoheptose. D-Mannose is an aldohexose.
16-3. a. enantiomers **b.** diastereomers
16-4. a. D-ribose **b.** L-talose **c.** L-allose **d.** L-ribose
16-5. D-psicose
16-6. a. $2^4 = 16$ **b.** $2^5 = 32$ **c.** none
16-7. D-psicose
16-11. a. the OH group at C-2 **b.** the OH group at C-2, C-3, and C-4 **c.** the OH group at C-3 and C-1
16-13. a. propyl β-D-alloside **b.** α-D-talose
16-14. A protonated amine is not a nucleophile.
16-15. −74.2
16-16. a. amylose has α-1,4′-glycosidic linkages; cellulose has β-1,4′-glycosidic linkages **b.** amylopectin has 1,6′-glycosidic linkages that create branches; amylose doesn't have branches **c.** glycogen has more branches than amylopectin **d.** chitin has an *N*-acetylamino group instead of an OH group at the 2-position.
16-17. a. From those with type A, B, or AB blood.
b. To those with type A, B, or O blood.

CHAPTER 17

17-2. Ile
17-4. because of the electron-withdrawing ammonium group

17-6. a. $HO\overset{O}{\overset{\|}{C}}CH_2CH_2\underset{\underset{^+NH_3}{|}}{C}H\overset{O}{\overset{\|}{C}}OH$

b. $HO\overset{O}{\overset{\|}{C}}CH_2CH_2\underset{\underset{^+NH_3}{|}}{C}H\overset{O}{\overset{\|}{C}}O^-$

c. $^-O\overset{O}{\overset{\|}{C}}CH_2CH_2\underset{\underset{^+NH_3}{|}}{C}H\overset{O}{\overset{\|}{C}}O^-$

d. $^-O\overset{O}{\overset{\|}{C}}CH_2CH_2\underset{\underset{NH_2}{|}}{C}H\overset{O}{\overset{\|}{C}}O^-$

17-7. a. 5.43 **b.** 10.76 **c.** 5.68 **d.** 2.98
17-8. a. Asp **b.** Arg
17-9. 2-methylpropanal
17-10. Leucine and isoleucine have similar polarities and pI values, so they show up as one spot.
17-13. a. L-Ala and D-Ala, L-Asp and D-Asp, L-Glu and D-Glu
b. L-Ala, L-Asp, L-Glu
17-14. a. leucine **b.** methionine
17-15. a. alanine **b.** isoleucine **c.** leucine
17-19. the bonds on either side of the α-carbon
17-21. Edman's reagent would release two amino acids in approximately equal amounts.
17-22. Gly-Arg-Trp-Ala-Glu-Leu-Met-Pro-Val-Asp
17-24. a. His-Lys, Leu-Val-Glu-Pro-Arg, Ala-Gly-Ala
b. Leu-Gly-Ser-Met-Phe-Pro-Tyr, Gly-Val
17-26. Leu-Tyr-Lys-Arg-Met-Phe-Arg-Ser
17-28. a. cigar-shaped protein **b.** subunit of a hexamer

CHAPTER 18

18-1. ~1
18-2. NAM
18-4. Arginine forms a direct hydrogen bond; lysine forms an indirect hydrogen bond.
18-5. 2, 3, and 4
18-7. 2
18-12. a. 7 **b.** 3 isolated from 2 others
18-13. N-5 is a stronger base because the lone pair on N-5, unlike the lone pair on N-1, cannot be delocalized onto an oxygen.
18-23. a. alanine **b.** aspartate
18-24. the one on the right
18-25. If the nitrogen is not protonated, it will be a poorer source for electron delocalization.
18-26. The hydrogen bond formed by the OH group weakens the bond to the α-carbon.
18-30. In THF, a carbonyl group is at C-4, and the bond between C-3 and C-4 is a single bond; in aminopterin, an amino group is at C-4, and the bond between C-3 and C-4 is a double bond.

CHAPTER 19

19-1. eight
19-2. seven
19-3. The β-carbon has a partial positive charge.
19-5. a. conversion of glucose to glucose-6-phosphate; conversion of fructose-6-phosphate to fructose-1,6-bisphosphate
b. conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate; conversion of phosphoenolpyruvate to pyruvate
19-7. two
19-8. acetaldehyde reductase
19-9. a ketone
19-11. pyruvate
19-13. a secondary alcohol
19-14. citrate and isocitrate
19-15. succinyl
19-16. a. 1 **b.** 1 + 5 = 6
19-17. a. glycerol kinase **b.** phosphatidic acid phosphatase

CHAPTER 20

20-2. glycerol tripalmitate
20-10. The two halves are synthesized in a head-to-tail fashion and then joined together in a tail-to-tail linkage.
20-14. The reaction of dimethylallyl pyrophosphate and isopentenyl pyrophosphate is an S_N1 reaction.
20-15. two 1,2-hydride shifts; two 1,2-methyl shifts

CHAPTER 21

21-2. a. 3′—C—C—T—G—T—T—A—G—A—C—G—5′ **b.** guanine
21-5. Thymine and uracil have the hydrogen bond donor and the hydrogen bond acceptor in the same place.
21-6. Met-Asp-Pro-Val-Ile-Lys-His
21-7. Met-Asp-Pro-Leu-Leu-Asn
21-9. the third base
21-10. 5′—G-C-A-T-G-G-A-C-C-C-C-G-T-T-A-T-T-A-A-A-C-A-C—3′

21-12.

xanthine

hypoxanthine

21-14. A

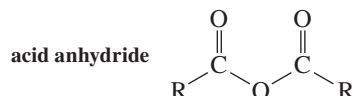
Glossary

absorption band a peak in a spectrum that occurs as a result of the absorption of energy.

acetal $R-C(OR)_2-H$ or $R-C(OR)_2-R$

achiral (optically inactive) an achiral molecule has a conformation identical to (superimposable upon) its mirror image.

acid (Brønsted) a species that loses a proton.

acid anhydride $R-C(=O)-O-C(=O)-R$

acid–base reaction a reaction in which an acid donates a proton to a base or accepts a share in a base's electrons.

acid catalyst a catalyst that increases the rate of a reaction by donating a proton.

acid-catalyzed reaction a reaction catalyzed by an acid.

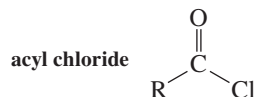
acid dissociation constant a measure of the degree to which an acid dissociates in solution.

active site a pocket or cleft in an enzyme where the substrate is bound.

acyclic noncyclic.

acyl adenylate a carboxylic acid derivative with AMP as the leaving group.

acyl–enzyme intermediate an intermediate formed when an amino acid residue of an enzyme is acetylated.

acyl chloride $R-C(=O)-Cl$

acyl group a carbonyl group bonded to an alkyl group or to an aryl group.

acyl phosphate a carboxylic acid derivative with a phosphate leaving group.

acyl pyrophosphate a carboxylic acid derivative with a pyrophosphate leaving group.

1,2-addition (direct addition) addition to the 1- and 2-positions of a conjugated system.

1,4-addition (conjugate addition) addition to the 1- and 4-positions of a conjugated system.

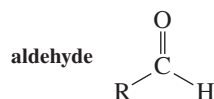
addition polymer (chain-growth polymer) a polymer made by adding monomers to the growing end of a chain.

addition reaction a reaction in which atoms or groups are added to the reactant.

adrenal cortical steroids glucocorticoids and mineralocorticoids.

alcohol a compound with an OH group in place of one of the hydrogens of an alkane (ROH).

alcoholysis reaction with an alcohol.

aldehyde $R-C(=O)-H$

aldol addition a reaction between two molecules of an aldehyde (or two molecules of a ketone) that connects the α-carbon of one with the carbonyl carbon of the other.

aldol condensation an aldol addition followed by the elimination of water.

aldose a polyhydroxyaldehyde.

aliphatic a nonaromatic organic compound.

alkaloid a natural product, with one or more nitrogen heteroatoms, found in the leaves, bark, or seeds of plants.

alkane a hydrocarbon that contains only single bonds.

alkene a hydrocarbon that contains a double bond.

alkylation reaction a reaction that adds an alkyl group to a reactant.

alkyl halide a compound with a halogen in place of one of the hydrogens of an alkane.

alkyl substituent (alkyl group) formed by removing a hydrogen from an alkane.

alkyne a hydrocarbon that contains a triple bond.

allene a compound with two adjacent double bonds.

allosteric activator a compound that activates an enzyme when it binds to a site on the enzyme (other than the active site).

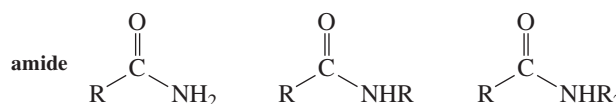
allosteric inhibitor a compound that inactivates an enzyme when it binds to a site on the enzyme (other than the active site).

allyl group $CH_2{=}CHCH_2-$

allylic carbon an sp^3 carbon adjacent to a vinylic carbon.

allylic cation a species with a positive charge on an allylic carbon.

alternating copolymer a copolymer in which two monomers alternate.

amide $R-C(=O)-NH_2$ $\quad R-C(=O)-NHR$ $\quad R-C(=O)-NHR_2$

amine a compound with a nitrogen in place of one of the hydrogens of an alkane (RNH_2, R_2NH, R_3N) .

amine inversion the configuration of an sp^3 hybridized nitrogen with a nonbonding pair of electrons that rapidly turns inside out.

amino acid an α-aminocarboxylic acid. Naturally occurring amino acids have the L configuration.

amino acid analyzer an instrument that automates the ion-exchange separation of amino acids.

amino acid residue a monomeric unit of a peptide or protein.

aminolysis reaction with an amine.

amino sugar a sugar in which one of the OH groups is replaced by an NH_2 group.

anabolic steroids steroids that aid in the development of muscle.

anabolism reactions that living organisms carry out in order to synthesize complex molecules from simple precursor molecules.

androgens male sex hormones.

angle strain the strain introduced into a molecule as a result of its bond angles being distorted from their ideal values.

angstrom unit of length; 100 picometers $= 10^{-8}$ cm $=$ 1 angstrom.

anion-exchange resin a positively charged resin used in ion-exchange chromatography.

anionic polymerization chain-growth polymerization in which the initiator is a nucleophile; the propagation site, therefore, is an anion.

anomeric carbon the carbon in a cyclic sugar that is the carbonyl carbon in the open-chain form.

anomers two cyclic sugars that differ in configuration only at the carbon that is the carbonyl carbon in the open-chain form.

antibiotic a compound that interferes with the growth of a microorganism.

antibodies compounds that recognize foreign particles in the body.

anticodon the three bases at the bottom of the middle loop in tRNA.

anti conformer the most stable of the staggered conformers.

antigens compounds that can generate a response from the immune system.

antisense strand (template strand) the strand in DNA that is read during transcription.

antiviral drug a drug that interferes with DNA or RNA synthesis in order to prevent a virus from replicating.

applied magnetic field the externally applied magnetic field.

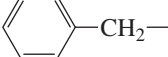
aramide an aromatic polyamide.

arene oxide an aromatic compound that has had one of its double bonds converted to an epoxide.

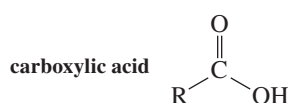
aromatic a cyclic and planar compound with an uninterrupted ring of *p* orbital-bearing atoms containing an odd number of pairs of π electrons.

aryl group a benzene or a substituted-benzene group.

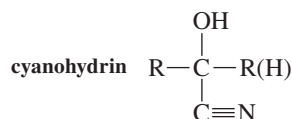
asymmetric center an atom bonded to four different atoms or groups.

atactic polymer a polymer in which the substituents are randomly oriented on the extended carbon chain.
atomic number the number of protons (or electrons) that the neutral atom has.
atomic orbital an orbital associated with an atom.
atomic weight the average mass of the atoms in the naturally occurring element.
axial bond a bond of the chair conformation of cyclohexane that is perpendicular to the plane in which the chair is drawn (an up–down bond).
back-side attack nucleophilic attack on the side of the carbon opposite the side bonded to the leaving group.
basal metabolic rate the number of calories that would be burned if one stayed in bed all day.
base[1] a species that gains a proton.
base[2] a purine or a pyrimidine in DNA and RNA.
base catalyst a catalyst that increases the rate of a reaction by removing a proton.
base peak the peak with the greatest abundance in a mass spectrum.
basicity the tendency of a compound to share its electrons with a proton.
bending vibration a vibration that does not occur along the line of the bond. It results in changing bond angles.

benzyl group

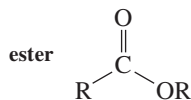
benzylic carbon an sp^3 hybridized carbon bonded to a benzene ring.
benzylic cation a compound with a positive charge on a benzylic carbon.
bifunctional molecule a molecule with two functional groups.
bile acids steroids that act as emulsifying agents so that water-insoluble compounds can be digested.
bimolecular reaction (second-order reaction) a reaction whose rate depends on the concentration of two reactants.
biochemistry (biological chemistry) the chemistry of biological systems.
biodegradable polymer a polymer that can be broken into small segments by an enzyme-catalyzed reaction.
bioorganic compound an organic compound found in biological systems.
biopolymer a polymer that is synthesized in nature.
biosynthesis synthesis in a biological system.
biotin the coenzyme required by enzymes that catalyze carboxylation of a carbon adjacent to an ester or a keto group.
block copolymer a copolymer in which there are regions (blocks) of each kind of monomer.
boat conformation the conformation of cyclohexane that roughly resembles a boat.
boiling point the temperature at which the vapor pressure from a liquid equals the atmospheric pressure.
bond length the internuclear distance between two atoms at minimum energy (maximum stability).
bond order the number of covalent bonds shared by two atoms.
bond strength the energy required to break a bond homolytically.
brand name (proprietary name, trade name) identifies a commercial product and distinguishes it from other products. It can be used only by the owner of the registered trademark.
Brønsted acid a species that loses a proton.
Brønsted base a species that gains a proton.
buffer a weak acid and its conjugate base.
carbanion a compound containing a negatively charged carbon.
carbocation a species containing a positively charged carbon.
carbocation rearrangement the rearrangement of a carbocation to a more stable carbocation.
carbohydrate a sugar or a saccharide. Naturally occurring carbohydrates have the D configuration.
α-carbon a carbon bonded to a leaving group or adjacent to a carbonyl carbon.
β-carbon a carbon adjacent to an α-carbon.
carbon acid a compound containing a carbon that is bonded to a relatively acidic hydrogen.
carbonyl carbon the carbon of a carbonyl group.
carbonyl compound a compound that contains a carbonyl group.
carbonyl group a carbon doubly bonded to an oxygen.
carbonyl oxygen the oxygen of a carbonyl group.
carboxyl group COOH

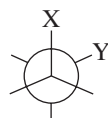
carboxylic acid $R-\overset{\overset{\large O}{\|}}{C}-OH$

carboxylic acid derivative a compound that is hydrolyzed to a carboxylic acid.
carboxyl oxygen the single-bonded oxygen of a carboxylic acid or an ester.
carotenoid a class of compounds (a tetraterpene) responsible for the red and orange colors of fruits, vegetables, and fall leaves.
catabolism reactions that living organisms carry out in order to break down complex molecules into simple molecules and energy.
catalyst a species that increases the rate at which a reaction occurs without being consumed in the reaction. Because it does not change the equilibrium constant of the reaction, it does not change the amount of product that is formed.
catalytic hydrogenation the addition of hydrogen to a double or a triple bond with the aid of a metal catalyst.
cation-exchange resin a negatively charged resin used in ion-exchange chromatography.
cationic polymerization chain-growth polymerization in which the initiator is an electrophile; the propagation site, therefore, is a cation.
cephalin a phosphoacylglycerol in which the second OH group of phosphate has formed an ester with ethanolamine.
cerebroside a sphingolipid in which the terminal OH group of sphingosine is bonded to a sugar residue.
chain-growth polymer (addition polymer) a polymer made by adding monomers to the growing end of a chain.
chain transfer a growing polymer chain reacts with a molecule XY in a manner that allows X to terminate the chain, leaving behind Y to initiate a new chain.
chair conformation the conformation of cyclohexane that roughly resembles a chair. It is the most stable conformation of cyclohexane.
chemically equivalent protons protons with the same connectivity relationship to the rest of the molecule.
chemical shift the location of a signal in an NMR spectrum. It is measured downfield from a reference compound (most often, TMS).
chiral (optically active) a chiral molecule has a nonsuperimposable mirror image.
chiral center a tetrahedral atom bonded to four different groups.
cholesterol a steroid that is the precursor of all other animal steroids.
chromatography a separation technique in which the mixture to be separated is dissolved in a solvent and the solvent is passed through a column packed with an absorbent stationary phase.
cis fused two cyclohexane rings fused together such that if the second ring were considered to be two substituents of the first ring, one substituent would be in an axial position and the other would be in an equatorial position.
cis isomer the isomer with the hydrogens on the same side of the double bond or cyclic structure.
cis–trans isomers geometric isomers.
citric acid cycle (Krebs cycle) a series of reactions that converts the acetyl group of acetyl-CoA into two molecules of CO_2.
Claisen condensation a reaction between two molecules of an ester that connects the α-carbon of one with the carbonyl carbon of the other and eliminates an alkoxide ion.
α-cleavage homolytic cleavage of an alpha substituent.
codon a sequence of three bases in mRNA that specifies the amino acid to be incorporated into a protein.
coenzyme a cofactor that is an organic molecule.
coenzyme A a thiol used by biological organisms to form thioesters.
coenzyme B_{12} the coenzyme required by enzymes that catalyze certain rearrangement reactions.
coil conformation (loop conformation) that part of a protein that is highly ordered, but not in an α-helix or a β-pleated sheet.
common name nonsystematic nomenclature.
competitive inhibitor a compound that inhibits an enzyme by competing with the substrate for binding at the active site.
complete racemization the formation of a pair of enantiomers in equal amounts.
complex carbohydrate a carbohydrate containing two or more sugar molecules linked together.
concerted reaction a reaction in which all the bond-making and bond-breaking processes occur in one step.
condensation polymer (step-growth polymer) a polymer made by combining two molecules while removing a small molecule (usually water or an alcohol).

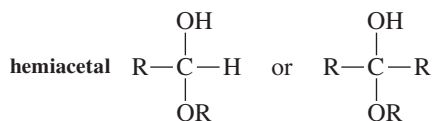
condensation reaction a reaction combining two molecules while removing a small molecule (usually water or an alcohol).
conducting polymer a polymer that can conduct electricity.
configuration the three-dimensional structure of a particular atom in a compound. The configuration is designated by *R* or *S*.
configurational isomers stereoisomers that cannot interconvert unless a covalent bond is broken. Cis–trans isomers and optical isomers are configurational isomers.
conformation the three-dimensional shape of a molecule at a given instant that can change as a result of rotations about σ bonds.
conformers different conformations of a molecule.
conjugate acid a species accepts a proton to form its conjugate acid.
conjugate addition 1,4-addition to an α,β-unsaturated carbonyl compound.
conjugate base a species loses a proton to form its conjugate base.
conjugated double bonds double bonds separated by one single bond.
constitutional isomers (structural isomers) molecules that have the same molecular formula but differ in the way their atoms are connected.
contributing resonance structure (resonance contributor, resonance structure) a structure with localized electrons that approximates the structure of a compound with delocalized electrons.
copolymer a polymer formed from two or more different monomers.
coupled protons protons that split each other. Coupled protons have the same coupling constant.
coupled reaction an endergonic reaction followed by an exergonic reaction.
covalent bond a bond created as a result of sharing electrons.
crossed aldol addition an aldol addition in which two different aldehydes or ketones are used.
crossed Claisen condensation a Claisen condensation in which two different esters are used.
cross-linking connecting polymer chains by intermolecular bond formation.
C-terminal amino acid the terminal amino acid of a peptide (or protein) that has a free carboxyl group.

cyanohydrin R—C(OH)(C≡N)—R(H)

cycloalkane an alkane with its carbon chain arranged in a closed ring.
deamination loss of ammonia.
decarboxylation loss of carbon dioxide.
dehydration loss of water.
dehydrogenase an enzyme that carries out an oxidation reaction by removing hydrogen from the substrate.
dehydrohalogenation elimination of a proton and a halide ion.
delocalization energy (resonance energy) the extra stability a compound achieves as a result of having delocalized electrons.
delocalized electrons electrons that are shared by more than two atoms.
denaturation destruction of the highly organized tertiary structure of a protein.
deoxygenation removal of an oxygen from a reactant.
deoxyribonucleic acid (DNA) a polymer of deoxyribonucleotides.
deoxyribonucleotide a nucleotide in which the sugar component is D-2′-deoxyribose.
deoxy sugar a sugar in which one of the OH groups has been replaced by an H.
detergent a salt of a sulfonic acid.
dextrorotatory the enantiomer that rotates polarized light in a clockwise direction.
diastereomer a configurational stereoisomer that is not an enantiomer.
1,3-diaxial interaction the interaction between an axial substituent and the other two axial substituents on the same side of the cyclohexane ring.
Diels–Alder reaction a [4 + 2] cycloaddition reaction.
diene a hydrocarbon with two double bonds.
dienophile an alkene that reacts with a diene in a Diels–Alder reaction.
***β*-diketone** a ketone with a second carbonyl group at the β-position.
dimer a molecule formed by the joining together of two identical molecules.
dinucleotide two nucleotides linked by phosphodiester bonds.
dipeptide two amino acids linked by an amide bond.
dipole–dipole interaction an interaction between the dipole of one molecule and the dipole of another.
dipole moment (μ) a measure of the separation of charge in a bond or in a molecule.
direct addition 1,2-addition to an α,β-unsaturated carbonyl compound (addition to the carbonyl carbon).
disaccharide a compound containing two sugar molecules linked together.
disproportionation transfer of a hydrogen atom by a radical to another radical, forming an alkane and an alkene.
dissociation energy the amount of energy required to break a bond, or the amount of energy released when a bond is formed.
disulfide bridge a disulfide (—S—S—) bond in a peptide or protein.
DNA (deoxyribonucleic acid) a polymer of deoxyribonucleotides.
doping adding or removing electrons from a polymer with conjugated double bonds.
double bond a σ bond and a π bond between two atoms.
doublet an NMR signal split into two peaks.
doublet of doublets an NMR signal split into four peaks of approximately equal height. Caused by splitting a signal into a doublet by one hydrogen and into another doublet by another (nonequivalent) hydrogen.
drug a compound that reacts with a biological molecule, triggering a physiological effect.
drug resistance biological resistance to a particular drug.
eclipsed conformation a conformation in which the bonds on adjacent carbons are aligned as viewed looking down the carbon–carbon bond.
***E* conformation** the conformation of a carboxylic acid or carboxylic acid derivative in which the carbonyl oxygen and the substituent bonded to the carboxyl oxygen or nitrogen are on opposite sides of the single bond.
Edman's reagent phenyl isothiocyanate. A reagent used to determine the N-terminal amino acid of a polypeptide.
effective magnetic field the magnetic field that a proton "senses" through the surrounding cloud of electrons.
***E* isomer** the isomer with the high-priority groups on opposite sides of the double bond.
electromagnetic radiation radiant energy that displays wave properties.
electronegative element an element that readily acquires an electron.
electronegativity tendency of an atom to pull electrons toward itself.
electron sink site to which electrons can be delocalized.
electrophile an electron-deficient atom or molecule.
electrophilic addition reaction an addition reaction in which the first species that adds to the reactant is an electrophile.
electrophilic aromatic substitution a reaction in which an electrophile substitutes for a hydrogen of an aromatic ring.
electrophilic catalysis catalysis in which the species that facilitates the reaction is an electrophile.
electrophoresis a technique that separates amino acids on the basis of their pI values.
electrostatic attraction attractive force between opposite charges.
electrostatic catalysis stabilization of a charge by an opposite charge.
elimination reaction a reaction that involves the elimination of atoms (or molecules) from the reactant.
enantiomers nonsuperimposable mirror-image molecules.
endergonic reaction a reaction with a positive $\Delta G°$.
endopeptidase an enzyme that hydrolyzes a peptide bond that is not at the end of a peptide chain.
endothermic reaction a reaction with a positive $\Delta H°$.
enediol rearrangement interconversion of an aldose and one or more ketoses.
enkephalins pentapeptides synthesized by the body to control pain.
enolization keto–enol interconversion.
enthalpy the heat given off ($-\Delta H°$) or the heat absorbed ($+\Delta H°$) during the course of a reaction.
entropy a measure of the freedom of motion in a system.
enzyme a protein that is a catalyst.
epimerization changing the configuration of an asymmetric center by removing a proton from it and then reprotonating the molecule at the same site.
epimers monosaccharides that differ in configuration at only one carbon.
epoxidation formation of an epoxide.
epoxide an ether in which the oxygen is incorporated into a three-membered ring.
epoxy resin substance formed by mixing a low-molecular-weight prepolymer with a compound that forms a cross-linked polymer.
equatorial bond a bond of the chair conformer of cyclohexane that juts out from the ring in approximately the same plane that contains the chair.

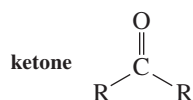
equilibrium constant the ratio of products to reactants at equilibrium or the ratio of the rate constants for the forward and reverse reactions.
E1 reaction an elimination reaction with a unimolecular transition state.
E2 reaction an elimination reaction with a bimolecular transition state.
essential amino acid an amino acid that humans must obtain from their diet because they cannot synthesize it at all or cannot synthesize it in adequate amounts.
essential oils fragrances and flavorings isolated from plants that do not leave residues when they evaporate. Most are terpenes.

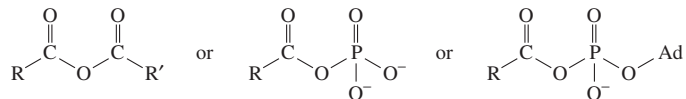
ester $RC(=O)OR$

estrogens (estrone and estradiol) female sex hormones.
ether a compound containing an oxygen bonded to two carbons (ROR).
exergonic reaction a reaction with a negative $\Delta G°$.
exopeptidase an enzyme that hydrolyzes a peptide bond at the end of a peptide chain.
exothermic reaction a reaction with a negative $\Delta H°$.
fat a triester of glycerol that exists as a solid at room temperature.
fatty acid a long-chain carboxylic acid.
feedback inhibitor a compound that inhibits a step at the beginning of the pathway for its biosynthesis.
fibrous protein a water-insoluble protein in which the polypeptide chains are arranged in bundles.
Fischer projection a method of representing the spatial arrangement of groups bonded to an asymmetric center. The asymmetric center is the point of intersection of two perpendicular lines; the horizontal lines represent bonds that project out of the plane of the paper toward the viewer, and the vertical lines represent bonds that point back from the plane of the paper away from the viewer.
flavin adenine dinucleotide (FAD) a coenzyme required in certain oxidation reactions. It is reduced to $FADH_2$, which forms 1.5 ATPs in oxidative phosphorylation when it is oxidized back to FAD.
formal charge the number of valence electrons – (the number of nonbonding electrons + 1/2 the number of bonding electrons).
free energy of activation ($\Delta G^{\ddagger}$) the true energy barrier to a reaction.
frequency the velocity of a wave divided by its wavelength (in units of cycles/s).
Friedel–Crafts acylation an electrophilic substitution reaction that puts an acyl group on a benzene ring.
Friedel–Crafts alkylation an electrophilic substitution reaction that puts an alkyl group on a benzene ring.
functional group the center of reactivity in a molecule.
furanose a five-membered-ring sugar.
furanoside a five-membered-ring glycoside.
gauche X and Y are gauche to each other in this Newman projection:

X
Y

gauche conformer a staggered conformer in which the largest substituents are gauche to each other.
gauche interaction the interaction between two atoms or groups that are gauche to each other.
gene a segment of DNA.
generic name a commercially nonrestricted name for a drug.
gene therapy a technique that inserts a synthetic gene into the DNA of an organism that is defective in that gene.
genetic code the amino acid specified by each three-base sequence of mRNA.
genetic engineering insertion of a segment of DNA into the DNA of a replicating host cell.
geometric isomers cis–trans (or *E,Z*) isomers.
Gibbs standard free-energy change ($\Delta G°$) the difference between the free-energy content of the products and the free-energy content of the reactants at equilibrium under standard conditions (1 M, 25 °C, 1 atm).
globular protein a water-soluble protein that tends to have a roughly spherical shape.
gluconeogenesis the synthesis of D-glucose from pyruvate.
glycolysis (glycolytic cycle) the series of reactions that converts D-glucose into two molecules of pyruvate.
glycoprotein a protein that is covalently bonded to a polysaccharide.
glycoside the acetal of a sugar.
***N*-glycoside** a glycoside with a nitrogen instead of an oxygen at the glycosidic linkage.
glycosidic bond the bond between the anomeric carbon and the alcohol in a glycoside.
α-1,4′-glycosidic linkage a linkage between the C-1 oxygen of one sugar and the C-4 of a second sugar with the oxygen atom of the glycosidic linkage in the axial position.
β-1,4′-glycosidic linkage a linkage between the C-1 oxygen of one sugar and the C-4 of a second sugar with the oxygen atom of the glycosidic linkage in the equatorial position.
genetically modified organism (GMO) insertion of a gene into the DNA of a species.
graft copolymer a copolymer that contains branches of a polymer of one monomer grafted onto the backbone of a polymer made from another monomer.
Grignard reagent the compound that results when magnesium is inserted between the carbon and halogen of an alkyl halide (RMgBr, RMgCl).
ground-state electronic configuration a description of which orbitals the electrons of an atom or molecule occupy when all of the electrons of atoms are in their lowest-energy orbitals.
half-chair conformation the least stable conformation of cyclohexane.
halogenation reaction with halogen (Br_2 or Cl_2).
Haworth projection a way to show the structure of a sugar; the five- and six-membered rings are represented as being flat.
head-to-tail addition the head of one molecule is added to the tail of another.
heat of hydrogenation the heat ($-\Delta H°$) released in a hydrogenation reaction.
α-helix the backbone of a polypeptide coiled in a right-handed spiral with hydrogen bonding occurring within the helix.

hemiacetal $R-CH(OH)(OR)$ or $R-CR(OH)(OR)$

heptose a monosaccharide with seven carbons.
hexose a monosaccharide with six carbons.
high-energy bond a bond that releases a great deal of energy when it is broken.
homolytic bond cleavage (homolysis) breaking a bond with the result that each of the atoms gets one of the bonding electrons.
homopolymer a polymer that contains only one kind of monomer.
hormone an organic compound synthesized in a gland and delivered by the bloodstream to its target tissue.
human genome the total DNA of a human cell.
hybrid orbital an orbital formed by mixing (hybridizing) orbitals.
hydrated water has been added to a compound.
hydration addition of water to a compound.
hydride ion a negatively charged hydrogen.
1,2-hydride shift the movement of a hydride ion from one carbon to an adjacent carbon.
hydrocarbon a compound that contains only carbon and hydrogen.
α-hydrogen usually, a hydrogen bonded to the carbon adjacent to a carbonyl carbon.
hydrogenation addition of hydrogen.
hydrogen bond an unusually strong dipole–dipole attraction (5 kcal/mol) between a hydrogen bonded to O, N, or F and the nonbonding electrons of an O, N, or F of another molecule.
hydrogen ion (proton) a positively charged hydrogen.
hydrolysis reaction with water.
hydrophobic interactions interactions between nonpolar groups. These interactions increase stability by decreasing the amount of structured water (increasing entropy).
hyperconjugation delocalization of electrons by overlap of carbon–hydrogen or carbon–carbon σ bonds with an empty *p* orbital.
imine (Schiff base) $R_2C=NR$
induced-dipole–induced-dipole interaction an interaction between a temporary dipole in one molecule and the dipole the temporary dipole induces in another molecule.
induced-fit model a model that describes the specificity of an enzyme for its substrate: the shape of the active site does not become completely complementary to the shape of the substrate until after the enzyme binds the substrate.
inductive electron donation donation of electrons through σ bonds.

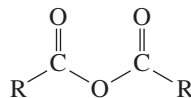
inductive electron withdrawal withdrawal of electrons through a σ bond.
informational strand (sense strand) the strand in DNA that is not read during transcription; it has the same sequence of bases as the synthesized mRNA strand (with a U, T difference).
infrared radiation electromagnetic radiation familiar to us as heat.
infrared spectroscopy uses infrared energy to provide a knowledge of the functional groups in a compound.
infrared (IR) spectrum a plot of percent transmission versus wavenumber (or wavelength) of infrared radiation.
initiation step the step in which radicals are created, or the step in which the radical needed for the first propagation step is created.
interchain disulfide bridge a disulfide bridge between two cysteine residues in different peptide chains.
intermediate a species formed during a reaction and that is not the final product of the reaction.
intermolecular reaction a reaction that takes place between two molecules.
internal alkyne an alkyne with the triple bond not at the end of the carbon chain.
intrachain disulfide bridge a disulfide bridge between two cysteine residues in the same peptide chain.
intramolecular reaction a reaction that takes place within a molecule.
inversion of configuration turning the configuration of a carbon inside out like an umbrella in a windstorm, so that the resulting product has a configuration opposite that of the reactant.
ion–dipole interaction the interaction between an ion and the dipole of a molecule.
ion-exchange chromatography a technique that uses a column packed with an insoluble resin to separate compounds on the basis of their charges and polarities.
ionic bond a bond formed through the attraction of two ions of opposite charges.
isoelectric point (pI) the pH at which there is no net charge on an amino acid.
isolated double bonds double bonds separated by more than one single bond.
isomers nonidentical compounds with the same molecular formula.
isoprene rule rule expressing the head-to-tail linkage of isoprene units.
isotactic polymer a polymer in which all the substituents are on the same side of the fully extended carbon chain.
isotopes atoms with the same number of protons but different numbers of neutrons.
IUPAC nomenclature systematic nomenclature of chemical compounds.
Kekulé structure a model that represents the bonds between atoms as lines.
keto–enol tautomerism (keto–enol interconversion) interconversion of keto and enol tautomers.
keto–enol tautomers a ketone and its isomeric α,β-unsaturated alcohol.
β-keto ester an ester with a second carbonyl group at the β-position.

ketone $\mathrm{R{-}C({=}O){-}R}$

ketose a polyhydroxyketone.
kinase an enzyme that puts a phosphate group on its substrate.
kinetic control when a reaction is under kinetic control, the relative amounts of the products depend on the rates at which they are formed.
kinetic product the product that is formed the fastest.
kinetic resolution separation of enantiomers on the basis of the difference in their rate of reaction with an enzyme.
kinetics the field of chemistry that deals with the rates of chemical reactions.
kinetic stability chemical reactivity, indicated by $\Delta G^{\ddagger}$. If $\Delta G^{\ddagger}$ is large, the compound is kinetically stable (not very reactive). If $\Delta G^{\ddagger}$ is small, the compound is kinetically unstable (highly reactive).
Krebs cycle (citric acid cycle, tricarboxylic acid cycle, TCA cycle) a series of reactions that convert the acetyl group of acetyl-CoA into two molecules of CO_2.
λ_{max} the wavelength at which there is maximum UV/Vis absorbance.
lead compound the prototype in a search for other biologically active compounds.
leaving group the group that is displaced in a nucleophilic substitution reaction.
Le Châtelier's principle states that if an equilibrium is disturbed, the components of the equilibrium will adjust in a way that will offset the disturbance.
lecithin a phosphoacylglycerol in which the second OH group of phosphate has formed an ester with choline.
levorotatory the enantiomer that rotates polarized light in a counterclockwise direction.
Lewis structure a model that represents the bonds between atoms as lines or dots and the valence electrons as dots.
lipid a water-insoluble compound found in a living system.
lipid bilayer two layers of phosphoacylglycerols arranged so that their polar heads are on the outside and their nonpolar fatty acid chains are on the inside.
lipoate a coenzyme required in certain oxidation reactions.
living polymer a nonterminated chain-growth polymer that remains active. This means that the polymerization reaction can continue upon the addition of more monomer.
localized electrons electrons that are restricted to a particular locality.
lock-and-key model a model that describes the specificity of an enzyme for its substrate: the substrate fits the enzyme as a key fits a lock.
lone-pair electrons (nonbonding electrons) valence electrons not used in bonding.
loop conformation (coil conformation) that part of a protein that is highly ordered, but not in an α-helix or β-pleated sheet.
magnetic resonance imaging (MRI) NMR used in medicine. The difference in the way water is bound in different tissues produces a variation in signal between organs as well as between healthy and diseased tissue.
major groove the wider and deeper of the two alternating grooves in DNA.
mass number the number of protons plus the number of neutrons in an atom.
mass spectrometry provides a knowledge of the molecular weight, molecular formula, and certain structural features of a compound.
mass spectrum a plot of the relative abundance of the positively charged fragments produced in a mass spectrometer versus their *m/z* values.
materials science the science of creating new materials to be used in place of known materials such as metal, glass, wood, cardboard, and paper.
mechanism-based inhibitor (suicide inhibitor) a compound that inactivates an enzyme by undergoing part of its normal catalytic mechanism.
mechanism of a reaction a description of the step-by-step process by which reactants are changed into products.
melting point the temperature at which a solid becomes a liquid.
membrane the material that surrounds a cell in order to isolate its contents.
mercaptan (thiol) the sulfur analog of an alcohol (RSH).
meso compound a compound that contains asymmetric centers and a plane of symmetry.
metabolism reactions that living organisms carry out in order to obtain the energy and to synthesize the compounds they require.
methine hydrogen a tertiary hydrogen.
methylene group a CH_2 group.
1,2-methyl shift the movement of a methyl group with its bonding electrons from one carbon to an adjacent carbon.
micelle a spherical aggregation of molecules, each with a long, hydrophobic tail and a polar head, arranged so that the polar head points to the outside of the sphere.
minor groove the narrower and more shallow of the two alternating grooves in DNA.
mixed anhydride an anhydride formed from two different acids.

$\mathrm{R{-}C({=}O){-}O{-}C({=}O){-}R'}$ or $\mathrm{R{-}C({=}O){-}O{-}P({=}O)(O^-){-}O^-}$ or $\mathrm{R{-}C({=}O){-}O{-}P({=}O)(O^-){-}O{-}Ad}$

mixed triacylglycerol a triacylglycerol in which the fatty-acid components are different.
molecular ion (parent ion) peak in the mass spectrum with the greatest *m/z*.
molecular orbital an orbital associated with a molecule.
molecular recognition the recognition of one molecule by another as a result of specific interactions; for example, the specificity of an enzyme for its substrate.
monomer a repeating unit in a polymer.
monosaccharide (simple carbohydrate) a single sugar molecule.
monoterpene a terpene that contains 10 carbons.
MRI scanner an NMR spectrometer used in medicine for whole-body NMR.
multiplet an NMR signal split into more than seven peaks.
multiplicity the number of peaks in an NMR signal.
mutarotation a slow change in optical rotation to an equilibrium value.
mutase an enzyme that transfers a group from from one position to another.
$N + 1$ rule an ^{1}H NMR signal for a hydrogen with N equivalent hydrogens bonded to an adjacent carbon is split into $N + 1$ peaks. A ^{13}C NMR signal for a carbon bonded to N hydrogens is split into $N + 1$ peaks.

natural-abundance atomic weight the average mass of the atoms in the naturally occurring element.
natural product a product synthesized in nature.
neurotransmitter a compound that transmits nerve impulses.
nicotinamide adenine dinucleotide (NAD^+) a coenzyme required in certain oxidation reactions. It is reduced to NADH, which forms 2.5 ATPs in oxidative phosphorylation when it is oxidized back to NAD^+.
nicotinamide adenine dinucleotide phosphate ($NADP^+$) a coenzyme that is reduced to NADPH, which is used as a reducing agent in anabolic reactions.
nitration substitution of a nitro group (NO_2) for a hydrogen of a benzene ring.
nitrile a compound that contains a carbon–nitrogen triple bond ($RC{\equiv}N$).
NMR spectroscopy the absorption of electromagnetic radiation to determine the structural features of an organic compound. In the case of NMR spectroscopy, it determines the carbon–hydrogen framework.
node that part of an orbital in which there is zero probability of finding an electron.
nominal mass mass rounded to the nearest whole number.
nonbonding electrons (lone-pair electrons) valence electrons not used in bonding.
noncovalent interaction an interaction between atoms (or molecules) that is weaker than a covalent bond.
nonpolar covalent bond a bond formed between two atoms that share the bonding electrons equally.
normal alkane (straight-chain alkane) an alkane in which the carbons form a contiguous chain with no branches.
***N*-phthalimidomalonic ester synthesis** a method used to synthesize an amino acid that combines the malonic ester synthesis and the Gabriel synthesis.
N-terminal amino acid the terminal amino acid of a peptide (or protein) that has a free amino group.
nucleic acid the two kinds of nucleic acid are DNA and RNA.
nucleophile an electron-rich atom or molecule.
nucleophilic acyl substitution reaction a reaction in which a group bonded to an acyl or aryl group is substituted by another group.
nucleophilic addition reaction a reaction that involves the addition of a nucleophile to a reagent.
nucleophilic catalysis (covalent catalysis) catalysis that occurs as a result of a nucleophile forming a covalent bond with one of the reactants.
nucleophilic catalyst a catalyst that increases the rate of a reaction by acting as a nucleophile.
nucleophilicity a measure of how readily an atom or a molecule with a pair of nonbonding electrons attacks an atom.
nucleophilic substitution reaction a reaction in which a nucleophile substitutes for an atom or a group.
nucleoside a heterocyclic base (a purine or a pyrimidine) bonded to the anomeric carbon of a sugar (D-ribose or D-2′-deoxyribose).
nucleotide a heterocycle attached in the β-position to a phosphorylated ribose or deoxyribose.
observed rotation the amount of rotation observed in a polarimeter.
octet rule states that an atom will give up, accept, or share electrons in order to achieve a filled shell. Because a filled second shell contains eight electrons, this is known as the octet rule.
oil a triester of glycerol that exists as a liquid at room temperature.
olefin an alkene.
oligomer a protein with more than one peptide chain.
oligonucleotide 3 to 10 nucleotides linked by phosphodiester bonds.
oligopeptide 3 to 10 amino acids linked by amide bonds.
oligosaccharide 3 to 10 sugar molecules linked by glycosidic bonds.
open-chain compound an acyclic compound.
operating frequency the frequency at which an NMR spectrometer operates.
optical isomers stereoisomers that contain chirality centers.
optically active rotates the plane of polarized light.
optically inactive does not rotate the plane of polarized light.
orbital the volume of space around the nucleus in which an electron is most likely to be found.
orbital hybridization mixing of orbitals.
organic compound a compound that contains carbon.
organic synthesis preparation of organic compounds from other organic compounds.
organometallic compound a compound containing a carbon–metal bond.
oxidation loss of electrons by an atom or a molecule.
β-oxidation a series of four reactions that removes two carbons from a fatty acyl-CoA.
oxidation reaction a reaction in which the number of C—H bonds decreases or the number of C—O, C—N, or C—X (X = a halogen) increases.
oxidative phosphorylation a series of reactions that converts a molecule of NADH and a molecule of $FADH_2$ into 2.5 and 1.5 molecules of ATP, respectively.
oxyanion a compound with a negatively charged oxygen.
paraffin an alkane.
parent hydrocarbon the longest continuous carbon chain in a molecule.
parent ion (molecular ion) peak in the mass spectrum with the greatest *m/z*.
partial hydrolysis a technique that hydrolyzes only some of the peptide bonds in a polypeptide.
pentose a monosaccharide with five carbons.
peptide polymer of amino acids linked together by amide bonds. A peptide contains fewer amino acid residues than a protein does.
peptide bond the amide bond that links the amino acids in a peptide or protein.
peroxyacid a carboxylic acid with an OOH group instead of an OH group.
perspective formula a method of representing the spatial arrangement of groups bonded to an asymmetric center. Two bonds are drawn in the plane of the paper; a solid wedge is used to depict a bond that projects out of the plane of the paper toward the viewer, and a hatched wedge is used to represent a bond that projects back from the plane of the paper away from the viewer.
pH the pH scale is used to describe the acidity of a solution ($pH = -\log[H^+]$).
phenyl group $C_6H_5—$
pheromone a compound secreted by an animal that stimulates a physiological or behavioral response from a member of the same species.
phosphatase an enzyme that removes a phosphate group from its substrate.
phosphatidic acid a phosphoacylglycerol in which only one of the OH groups of phosphate is in an ester linkage.
phosphoacylglycerol (phosphoglyceride) a compound formed when two OH groups of glycerol form esters with fatty acids and the terminal OH group forms a phosphate ester.
phosphoanhydride bond the bond holding two phosphoric acid molecules together.
phospholipid a lipid that contains a phosphate group.
phosphoryl transfer reaction the transfer of a phosphate group from one compound to another.
photosynthesis the synthesis of glucose and O_2 from CO_2 and H_2O.
pi (π) bond a bond formed as a result of side-to-side overlap of *p* orbitals.
pinacol rearrangement rearrangement of a vicinal diol.
pK_a describes the tendency of a compound to lose a proton ($pK_a = -\log K_a$, where K_a is the acid dissociation constant).
plane of symmetry an imaginary plane that bisects a molecule into mirror images.
plasticizer an organic molecule that dissolves in a polymer and allows the polymer chains to slide by each other.
β-pleated sheet the backbone of a polypeptide that is extended in a zigzag structure with hydrogen bonding between neighboring chains.
polar covalent bond a covalent bond between atoms of different electronegativites.
polarimeter an instrument that measures the rotation of polarized light.
polarized light light that oscillates only in one plane.
polyamide a polymer in which the monomers are amides.
polycarbonate a step-growth polymer in which the dicarboxylic acid is carbonic acid.
polyester a polymer in which the monomers are esters.
polymer a large molecule made by linking monomers together.
polymer chemistry the field of chemistry that deals with synthetic polymers; part of the larger discipline known as materials science.
polymerization the process of linking up monomers to form a polymer.
polynucleotide many nucleotides linked by phosphodiester bonds.
polypeptide many amino acids linked by amide bonds.
polysaccharide a compound containing more than 10 sugar molecules linked together.
polyunsaturated fatty acid a fatty acid with more than one double bond.
polyurethane a polymer in which the monomers are urethanes.

porphyrin ring system consists of four pyrrole rings joined by one-carbon bridges.
primary alcohol an alcohol in which the OH group is bonded to a primary carbon.
primary alkyl halide an alkyl halide in which the halogen is bonded to a primary carbon.
primary alkyl radical a radical with the unpaired electron on a primary carbon.
primary amine an amine with one alkyl group bonded to the nitrogen.
primary carbocation a carbocation with the positive charge on a primary carbon.
primary carbon a carbon bonded to only one other carbon.
primary hydrogen a hydrogen bonded to a primary carbon.
primary structure (of a nucleic acid) the sequence of bases in a nucleic acid.
primary structure (of a protein) the sequence of amino acids in a protein.
promoter site a short sequence of bases at the beginning of a gene.
propagating site the reactive end of a chain-growth polymer.
propagation step in the first of a pair of propagation steps, a radical (or an electrophile or a nucleophile) reacts to produce another radical (or an electrophile or a nucleophile) that reacts in the second to produce the radical (or the electrophile or the nucleophile) that was the reactant in the first propagation step.
prostacyclin a lipid, derived from arachidonic acid, that dilates blood vessels and inhibits platelet aggregation.
protecting group a reagent that protects a functional group from a synthetic operation that it would otherwise not survive.
protein a polymer containing 40 to 4000 amino acids linked by amide bonds.
proton a positively charged hydrogen (H^+); a positively charged particle in an atomic nucleus.
proton-decoupled ^{13}C NMR spectrum a ^{13}C NMR spectrum in which all the signals appear as singlets because there is no coupling between the nucleus and its bonded hydrogens.
proton transfer reaction a reaction in which a proton is transferred from an acid to a base.
protoporphyrin IX the porphyrin ring system of heme.
pyranose a six-membered-ring sugar.
pyranoside a six-membered-ring glycoside.
pyridoxal phosphate the coenzyme required by enzymes that catalyze certain transformations of amino acids.
pyrosequencing a technique used to determine the sequence of bases in a polynucleotide by detecting the identity of each base that adds to a primer.
quartet an NMR signal split into four peaks.
quaternary structure a description of the way the individual polypeptide chains of a protein are arranged with respect to each other.
racemic mixture (racemate) a mixture of equal amounts of a pair of enantiomers.
radical an atom or a molecule with an unpaired electron.
radical chain reaction a reaction in which radicals are formed and react in repeating propagating steps.
radical inhibitor a compound that traps radicals.
radical initiator a compound that creates radicals.
radical polymerization chain-growth polymerization in which the initiator is a radical; the propagation site is, therefore, a radical.
radical reaction a reaction in which a new bond is formed by using one electron from one reagent and one electron from another reagent.
radical substitution reaction a substitution reaction that has a radical intermediate.
random coil the conformation of a totally denatured protein.
random copolymer a copolymer with a random distribution of monomers.
random screen (blind screen) the search for a pharmacologically active compound without any information about what chemical structures might show activity.
rate constant a measure of how easy or difficult it is to reach the transition state of a reaction (to get over the energy barrier to the reaction).
rate-determining step (rate-limiting step) the step in a reaction that has the transition state with the highest energy.
***R* configuration** after assigning relative priorities to the four groups bonded to an asymmetric center, if the lowest-priority group is on a vertical axis in a Fischer projection (or pointing away from the viewer in a perspective formula), an arrow drawn from the highest-priority group to the next-highest-priority group goes in a clockwise direction.
reaction coordinate diagram describes the energy changes that take place during the course of a reaction.
reactivity–selectivity principle states that the greater the reactivity of a species, the less selective the species will be.
recombinant DNA DNA that has been incorporated into a host cell.
reduction reaction a reaction in which the number of C—H bonds increases or the number of C—O, C—N, or C—X (X = a halogen) decreases.
reduction gain of electrons by an atom or a molecule.
reductive amination the reaction of an aldehyde or a ketone with ammonia or with a primary amine in the presence of a reducing agent (H_2, Pd/C).
reference compound a compound added to a sample whose NMR spectrum is to be taken. The positions of the signals in the NMR spectrum are measured from the position of the signal given by the reference compound.
regioselective reaction a reaction that leads to the preferential formation of one constitutional isomer over another.
regulatory enzyme an enzyme that can be turned on and off.
relative configuration the configuration of a compound relative to the configuration of another compound.
relative rate obtained by dividing the actual rate constant by the rate constant of the slowest reaction in the group being compared.
replication the synthesis of identical copies of DNA.
resolution of a racemic mixture separation of a racemic mixture into the individual enantiomers.
resonance a compound with delocalized electrons is said to have resonance.
resonance contributor (resonance structure, contributing resonance structure) a structure with localized electrons that approximates the true structure of a compound with delocalized electrons.
resonance electron donation donation of electrons through *p* orbital overlap with neighboring π bonds.
resonance electron withdrawal withdrawal of electrons through *p* orbital overlap with neighboring π bonds.
resonance energy (delocalization energy) the extra stability associated with a compound as a result of its having delocalized electrons.
resonance hybrid the actual structure of a compound with delocalized electrons; it is represented by two or more structures with localized electrons.
restriction endonuclease an enzyme that cleaves DNA at a specific base sequence.
restriction fragment a fragment that is formed when DNA is cleaved by a restriction endonuclease.
retro Diels–Alder reaction a reverse Diels–Alder reaction.
retrosynthesis (retrosynthetic analysis) working backward (on paper) from the target molecule to available starting materials.
retrovirus a virus whose genetic information is stored in its RNA.
rf radiation radiation in the radiofrequency region of the electromagnetic spectrum.
ribonucleic acid (RNA) a polymer of ribonucleotides.
ribonucleotide a nucleotide in which the sugar component is D-ribose.
ribosome a particle composed of about 40% protein and 60% RNA on which protein biosynthesis takes place.
ring-expansion rearrangement rearrangement of a carbocation in which the positively charged carbon is bonded to a cyclic compound and, as a result of rearrangement, the size of the ring increases by one carbon.
ring-flip (chair–chair interconversion) the conversion of the chair conformer of cyclohexane into the other chair conformer. Bonds that are axial in one chair conformer are equatorial in the other.
ring-opening polymerization a chain-growth polymerization that involves opening the ring of the monomer.
RNA (ribonucleic acid) a polymer of ribonucleotides.
rule of 13 allows possible molecular formulas to be determined from the *m/z* value of the molecular ion.
saponification hydrolysis of an ester (such as a fat) under basic conditions.
saturated hydrocarbon a hydrocarbon that is completely saturated (i.e., contains no double or triple bonds) with hydrogen.
Schiff base (imine) $R_2C{=}NR$
***S* configuration** after assigning relative priorities to the four groups bonded to an asymmetric center, if the lowest-priority group is on a vertical axis in a Fischer projection (or pointing away from the viewer in a perspective formula), an arrow drawn from the highest-priority group to the next-highest-priority group goes in a counterclockwise direction.
secondary alcohol an alcohol in which the OH group is bonded to a secondary carbon.
secondary alkyl halide an alkyl halide in which the halogen is bonded to a secondary carbon.

secondary alkyl radical a radical with the unpaired electron on a secondary carbon.
secondary amine an amine with two alkyl groups bonded to the nitrogen.
secondary carbocation a carbocation with the positive charge on a secondary carbon.
secondary carbon a carbon bonded to two other carbons.
secondary hydrogen a hydrogen bonded to a secondary carbon.
secondary structure of a protein a description of the conformation of the backbone of a protein.
secondary structure of DNA the double helix.
semiconservative replication the mode of replication that results in a daughter molecule of DNA having one of the original DNA strands plus a newly synthesized strand.
sense strand (informational strand) the strand in DNA that is not read during transcription; it has the same sequence of bases as the synthesized mRNA strand (with a U and T difference).
separated charges a positive and a negative charge that can be neutralized by the movement of electrons.
sesquiterpene a terpene that contains 15 carbons.
shielding phenomenon caused by electron donation to the environment of a proton. The electrons shield the proton from the full effect of the applied magnetic field. The more a proton is shielded, the farther to the right its signal appears in an NMR spectrum.
sigma (σ) bond a bond with a cylindrically symmetrical distribution of electrons.
simple carbohydrate (monosaccharide) a single sugar molecule.
simple triacylglycerol a triacylglycerol in which the fatty acid components are the same.
single bond a σ bond.
singlet an unsplit NMR signal.
skeletal structure shows the carbon–carbon bonds as lines and does not show the carbon–hydrogen bonds.
S_N1 reaction a unimolecular nucleophilic substitution reaction.
S_N2 reaction a bimolecular nucleophilic substitution reaction.
soap a sodium or potassium salt of a fatty acid.
solvation the interaction between a solvent and another molecule (or ion).
solvolysis reaction with the solvent.
specific rotation the amount the plane of polarization of plane-polarized light will be rotated by a compound with a concentration of 1.0 g/mL in a sample tube 1.0 dm long.
spectroscopy study of the interaction of matter and electromagnetic radiation.
sphingolipid a lipid that contains sphingosine.
sphingomyelin a sphingolipid in which the terminal OH group of sphingosine is bonded to phosphocholine or phosphoethanolamine.
spin-coupled ^{13}C NMR spectrum a ^{13}C NMR spectrum in which each signal of a carbon is split by the hydrogens bonded to that carbon.
spin coupling the atom that gives rise to an NMR signal is coupled to the rest of the molecule.
spin decoupling the atom that gives rise to an NMR signal is decoupled from the rest of the molecule.
spin–spin coupling the splitting of a signal in an NMR spectrum described by the $N + 1$ rule.
α-spin state nuclei in this spin state have their magnetic moments oriented in the same direction as the applied magnetic field.
β-spin state nuclei in this spin state have their magnetic moments oriented opposite the direction of the applied magnetic field.
splitting diagram a diagram that describes the splitting of a set of protons.
squalene a triterpene that is a precursor of steroid molecules.
stacking interactions van der Waals interactions between the mutually induced dipoles of adjacent pairs of bases in DNA.
staggered conformation a conformation in which the bonds on one carbon bisect the bond angle on the adjacent carbon when viewed looking down the carbon–carbon bond.
step-growth polymer (condensation polymer) a polymer made by combining two molecules while removing a small molecule (usually water or an alcohol).
stereochemistry the field of chemistry that deals with the structures of molecules in three dimensions.
stereogenic center (stereocenter) an atom at which the interchange of two substituents produces a stereoisomer.
stereoisomers isomers that differ in the way their atoms are arranged in space.
steric effects effects due to the fact that groups occupy a certain volume of space.
steric hindrance refers to bulky groups at the site of a reaction that make it difficult for the reactants to approach each other.
steric strain (van der Waals strain, van der Waals repulsion) the repulsion between the electron cloud of an atom or a group of atoms and the electron cloud of another atom or group of atoms.
steroid a class of compounds that contains a steroid ring system.
stop codon a codon at which protein synthesis is stopped.
straight-chain alkane (normal alkane) an alkane in which the carbons form a continuous chain with no branches.
Strecker synthesis a method used to synthesize an amino acid: an aldehyde reacts with NH_3, forming an imine that is attacked by cyanide ion. Hydrolysis of the product gives an amino acid.
stretching frequency the frequency at which a stretching vibration occurs.
stretching vibration a vibration occurring along the line of a bond.
structural isomers (constitutional isomers) molecules that have the same molecular formula but differ in the way their atoms are connected.
structural protein a protein that gives strength to a biological structure.
α-substituent a substituent on the side of a steroid ring system opposite that of the angular methyl groups.
β-substituent a substituent on the same side of a steroid ring system as that of the angular methyl groups.
α-substitution reaction a reaction that puts a substituent on an α-carbon in place of an α-hydrogen.
substrate the reactant of an enzyme-catalyzed reaction.
subunit an individual chain of an oligomer.
suicide inhibitor (mechanism-based inhibitor) a compound that inactivates an enzyme by undergoing part of its normal catalytic mechanism.
sulfide (thioether) the sulfur analog of an ether (RSR).
sulfonation substitution of a hydrogen of a benzene ring by a sulfonic acid group (SO_3H).
symmetrical anhydride an acid anhydride with identical R groups:

symmetrical ether an ether with two identical substituents bonded to the oxygen.
syndiotactic polymer a polymer in which the substituents regularly alternate on both sides of the fully extended carbon chain.
synthetic polymer a polymer that is not synthesized in nature.
systematic nomenclature nomenclature based on structure.
target molecule desired end product of a synthesis.
tautomerism interconversion of tautomers.
tautomers rapidly equilibrating isomers that differ in the location of their bonding electrons.
template strand (antisense strand) the strand in DNA that is read during transcription.
terminal alkyne an alkyne with the triple bond at the end of the carbon chain.
termination step the step in which two radicals combine to produce a molecule in which all the electrons are paired.
terpene a lipid, isolated from a plant, that contains carbon atoms in multiples of five.
terpenoid a terpene that contains oxygen.
tertiary alcohol an alcohol in which the OH group is bonded to a tertiary carbon.
tertiary alkyl halide an alkyl halide in which the halogen is bonded to a tertiary carbon.
tertiary alkyl radical a radical with the unpaired electron on a tertiary carbon.
tertiary amine an amine with three alkyl groups bonded to the nitrogen.
tertiary carbocation a carbocation with the positive charge on a tertiary carbon.
tertiary carbon a carbon bonded to three other carbons.
tertiary hydrogen a hydrogen bonded to a tertiary carbon.
tertiary structure a description of the three-dimensional arrangement of all the atoms in a protein.
tetraene a hydrocarbon with four double bonds.
tetrahedral bond angle the bond angle (109.5°) formed by adjacent bonds of an sp^3 hybridized carbon.

tetrahedral carbon an sp^3 hybridized carbon; a carbon that forms covalent bonds by using four sp^3 hybridized orbitals.
tetrahedral intermediate the intermediate formed in a nucleophilic acyl substitution reaction.
tetrahydrofolate (THF) the coenzyme required by enzymes that catalyze reactions that donate a group containing a single carbon to their substrates.
tetraterpene a terpene that contains 40 carbons.
tetrose a monosaccharide with four carbons.
thermal cracking using heat to break a molecule apart.
thermodynamic control when a reaction is under thermodynamic control, the relative amounts of the products depend on their stabilities.
thermodynamic product the most stable product.
thermodynamics the field of chemistry that describes the properties of a system at equilibrium.
thermodynamic stability indicated by $\Delta G°$. If $\Delta G°$ is negative, the products are more stable than the reactants. If $\Delta G°$ is positive, the reactants are more stable than the products.
thiamine pyrophosphate (TPP) the coenzyme required by enzymes that catalyze a reaction that transfers an acyl group to a substrate.
thin-layer chromatography a technique that separates compounds on the basis of their polarity.
thioester the sulfur analogue of an ester: $R-C(=O)-SR$
thioether (sulfide) the sulfur analog of an ether (RSR).
thiol (mercaptan) the sulfur analog of an alcohol (RSH).
titration curve a plot of pH versus added equivalents of hydroxide ion.
trademark a registered name, symbol, or picture.
trade name (proprietary name, brand name) identifies a commercial product and distinguishes it from other products.
transamination a reaction in which an amino group is transferred from one compound to another.
transcription the synthesis of mRNA from a DNA blueprint.
transesterification reaction the reaction of an ester with an alcohol to form a different ester.
trans fused two cyclohexane rings fused together such that if the second ring were considered to be two substituents of the first ring, both substituents would be in equatorial positions.
transimination the reaction of a primary amine with an imine to form a new imine and a primary amine derived from the original imine.
trans isomer the isomer with the hydrogens on opposite sides of the double bond or cyclic structure; the isomer with identical substituents on opposite sides of the double bond.
transition state the highest point on a hill in a reaction coordinate diagram. In the transition state, bonds in the reactant that will break are partially broken and bonds in the product that will form are partially formed.
translation the synthesis of a protein from an mRNA blueprint.
triacylglycerol the compound formed when the three OH groups of glycerol are esterified with fatty acids.
triene a hydrocarbon with three double bonds.
trigonal planar carbon an sp^2 hybridized carbon.
triose a monosaccharide with three carbons.
tripeptide three amino acids linked by amide bonds.
triple bond a σ bond plus two π bonds.
triplet an NMR signal split into three peaks.
triterpene a terpene that contains 30 carbons.
twist-boat conformation (skew-boat conformation) a conformation of cyclohexane.
ultraviolet light electromagnetic radiation with wavelengths ranging from 180 to 400 nm.
unimolecular reaction a reaction whose rate depends on the concentration of one reactant.
unsaturated hydrocarbon a hydrocarbon that contains one or more double or triple bonds.
unsymmetrical ether an ether with two different substituents bonded to the oxygen.
urethane a compound with a carbonyl group that is both an amide and an ester.
UV/Vis spectroscopy the absorption of electromagnetic radiation in the ultraviolet and visible regions of the spectrum; used to determine information about conjugated systems.
valence electron an electron in an unfilled shell.
van der Waals forces (London forces) induced-dipole–induced-dipole interactions.
vector sum takes into account both the magnitudes and the directions of the bond dipoles.
vinyl group $CH_2{=}CH{-}$
vinylic carbon a carbon in a carbon–carbon double bond.
vinylic cation a compound with a positive charge on a vinylic carbon.
vinyl polymer a polymer in which the monomers are ethylene or a substituted ethylene.
visible light electromagnetic radiation with wavelengths ranging from 400 to 780 nm.
vitamin a substance needed in small amounts for normal body function that the body cannot synthesize at all or cannot synthesize in adequate amounts.
vitamin KH_2 the coenzyme required by the enzyme that catalyzes the carboxylation of glutamate side chains.
vulcanization heating rubber with sulfur to increase its hardness while maintaining its flexibility.
wave equation an equation that describes the behavior of each electron in an atom or a molecule.
wavelength distance from any point on one wave to the corresponding point on the next wave (usually in units of μm or nm).
wavenumber the number of waves in 1 cm.
wax an ester formed from a long-chain carboxylic acid and a long-chain alcohol.
wedge-and-dash structure a method of representing the spatial arrangement of groups. Wedges are used to represent bonds that point out of the plane of the paper toward the viewer, and dashed lines are used to represent bonds that point back from the plane of the paper away from the viewer.
Williamson ether synthesis formation of an ether from the reaction of an alkoxide ion with an alkyl halide.
Ziegler–Natta catalyst an aluminum–titanium initiator that controls the stereochemistry of a polymer.
***Z* isomer** the isomer with the high-priority groups on the same side of the double bond.
zwitterion a compound with a negative charge and a positive charge on nonadjacent atoms.

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pK_a Values

Compound	pK_a
$CH_3C{\equiv}\overset{+}{N}H$	−10.1
HI	−10
HBr	−9
$CH_3CH{=}\overset{+}{O}H$	−8
$CH_3C(=\overset{+}{O}H)CH_3$	−7.3
HCl	−7
$C_6H_5{-}SO_3H$	−6.5
$CH_3C(=\overset{+}{O}H)OCH_3$	−6.5
$CH_3C(=\overset{+}{O}H)OH$	−6.1
H_2SO_4	−5
protonated pyrrole ($\overset{+}{N}H$, ring CH_2)	−3.8
$CH_3CH_2\overset{+}{O}(H)CH_2CH_3$	−3.6
$CH_3CH_2\overset{+}{O}H_2$	−2.4
$CH_3\overset{+}{O}H_2$	−2.5
H_3O^+	−1.7
HNO_3	−1.3
CH_3SO_3H	−1.2
$CH_3C(=\overset{+}{O}H)NH_2$	0.0
F_3CCOH (C=O)	0.2
Cl_3CCOH (C=O)	0.64
$C_5H_5\overset{+}{N}{-}OH$ (pyridine ring)	0.79
$O_2N{-}C_6H_4{-}\overset{+}{N}H_3$	1.0
pyrimidinium ($\overset{+}{N}H$)	1.0
Cl_2CHCOH (C=O)	1.3
HSO_4^-	2.0
H_3PO_4	2.1
purinium ($H\overset{+}{N}$)	2.5
FCH_2COH (C=O)	2.7
$ClCH_2COH$ (C=O)	2.8
$BrCH_2COH$ (C=O)	2.9
ICH_2COH (C=O)	3.2
HF	3.2
HNO_2	3.4
$O_2N{-}C_6H_4{-}COH$ (C=O)	3.4
$HCOH$ (C=O)	3.8
$Br{-}C_6H_4{-}\overset{+}{N}H_3$	3.9
$Br{-}C_6H_4{-}COH$ (C=O)	4.0
$C_6H_5{-}COH$ (C=O)	4.2
$CH_3{-}C_6H_4{-}COH$ (C=O)	4.3
$CH_3O{-}C_6H_4{-}COH$ (C=O)	4.5
$C_6H_5{-}\overset{+}{N}H_3$	4.6
CH_3COH (C=O)	4.8
quinolinium ($\overset{+}{N}H$)	4.9
$CH_3{-}C_6H_4{-}\overset{+}{N}H_3$	5.1
pyridinium ($\overset{+}{N}H$)	5.2
$CH_3O{-}C_6H_4{-}\overset{+}{N}H_3$	5.3
$CH_3C(CH_3){=}\overset{+}{N}HCH_3$	5.5
CH_3CCH_2CH (both C=O)	5.9
$HO\overset{+}{N}H_3$	6.0
H_2CO_3	6.4
imidazolium ($H\overset{+}{N}$, NH)	6.8
H_2S	7.0
$O_2N{-}C_6H_4{-}OH$	7.1
$H_2PO_4^-$	7.2
$C_6H_5{-}SH$	7.8

[a]pK_a values are for the red H in each structure

(continued)

pK_a Values (continued)

Compound	pK_a	Compound	pK_a	Compound	pK_a
$(CH_2)_2\overset{+}{N}H_2$	8.0	$CH_3\overset{O}{C}CH_2\overset{O}{C}OCH_2CH_3$	10.7	C_4H_4NH	~17
$H_2N\overset{+}{N}H_3$	8.1	$CH_3\overset{+}{N}H_3$	10.7	$CH_3\overset{O}{C}H$	17
$CH_3\overset{O}{C}OOH$	8.2	$C_6H_{11}\overset{+}{N}H_3$	10.7	$(CH_3)_3COH$	18
$C_6H_4(CO)_2NH$	8.3	$(CH_3)_2\overset{+}{N}H_2$	10.7	$CH_3\overset{O}{C}CH_3$	20
$CH_3CH_2NO_2$	8.6	$(CH_2)_5\overset{+}{N}H_2$	11.1	$CH_3\overset{O}{C}OCH_2CH_3$	24.5
$CH_3\overset{O}{C}CH_2\overset{O}{C}CH_3$	8.9	$CH_3CH_2\overset{+}{N}H_3$	11.0	$HC{\equiv}CH$	25
$HC{\equiv}N$	9.1	$(CH_2)_4\overset{+}{N}H_2$	11.3	$CH_3C{\equiv}N$	25
$O(CH_2CH_2)_2\overset{+}{N}H_2$	9.3	$HOOH$	11.6	$CH_3\overset{O}{C}N(CH_3)_2$	30
$Cl{-}C_6H_4{-}OH$	9.4	HPO_4^{2-}	12.3	H_2	35
$\overset{+}{N}H_4$	9.4	CF_3CH_2OH	12.4	NH_3	36
$HOCH_2CH_2\overset{+}{N}H_3$	9.5	$CH_3CH_2O\overset{O}{C}CH_2\overset{O}{C}OCH_2CH_3$	13.3	$(CH_2)_4NH$	36
$H_3\overset{+}{N}CH_2\overset{O}{C}O^-$	9.8	$HC{\equiv}CCH_2OH$	13.5	CH_3NH_2	40
$C_6H_5{-}OH$	10.0	$H_2N\overset{O}{C}NH_2$	13.7	$C_6H_5{-}CH_3$	41
$CH_3{-}C_6H_4{-}OH$	10.2	$CH_3\overset{+}{N}(CH_3)_2CH_2CH_2OH$	13.9	C_6H_6	43
HCO_3^-	10.2	$C_3H_3N{-}NH$	14.4	$CH_2{=}CHCH_3$	43
CH_3NO_2	10.2	CH_3OH	15.5	$CH_2{=}CH_2$	44
$H_2N{-}C_6H_4{-}OH$	10.3	H_2O	15.7	C_3H_6	46
CH_3CH_2SH	10.5	CH_3CH_2OH	16.0	CH_4	60
$(CH_3)_3\overset{+}{N}H$	10.6	$CH_3\overset{O}{C}NH_2$	16	CH_3CH_3	> 60
		$C_6H_5{-}\overset{O}{C}CH_3$	16.0		

Periodic Table of the Elements

Main groups (1A–2A, 3A–8A); Transition metals (3B–2B)

Period	1A[a] 1	2A 2	3B 3	4B 4	5B 5	6B 6	7B 7	8B 8	8B 9	8B 10	1B 11	2B 12	3A 13	4A 14	5A 15	6A 16	7A 17	8A 18
1	1 **H** 1.00794																	2 **He** 4.002602
2	3 **Li** 6.941	4 **Be** 9.012182											5 **B** 10.811	6 **C** 12.0107	7 **N** 14.0067	8 **O** 15.9994	9 **F** 18.998403	10 **Ne** 20.1797
3	11 **Na** 22.989770	12 **Mg** 24.3050											13 **Al** 26.981538	14 **Si** 28.0855	15 **P** 30.973761	16 **S** 32.065	17 **Cl** 35.453	18 **Ar** 39.948
4	19 **K** 39.0983	20 **Ca** 40.078	21 **Sc** 44.955910	22 **Ti** 47.867	23 **V** 50.9415	24 **Cr** 51.9961	25 **Mn** 54.938049	26 **Fe** 55.845	27 **Co** 58.933200	28 **Ni** 58.6934	29 **Cu** 63.546	30 **Zn** 65.39	31 **Ga** 69.723	32 **Ge** 72.64	33 **As** 74.92160	34 **Se** 78.96	35 **Br** 79.904	36 **Kr** 83.80
5	37 **Rb** 85.4678	38 **Sr** 87.62	39 **Y** 88.90585	40 **Zr** 91.224	41 **Nb** 92.90638	42 **Mo** 95.94	43 **Tc** [98]	44 **Ru** 101.07	45 **Rh** 102.90550	46 **Pd** 106.42	47 **Ag** 107.8682	48 **Cd** 112.411	49 **In** 114.818	50 **Sn** 118.710	51 **Sb** 121.760	52 **Te** 127.60	53 **I** 126.90447	54 **Xe** 131.293
6	55 **Cs** 132.90545	56 **Ba** 137.327	71 **Lu** 174.967	72 **Hf** 178.49	73 **Ta** 180.9479	74 **W** 183.84	75 **Re** 186.207	76 **Os** 190.23	77 **Ir** 192.217	78 **Pt** 195.078	79 **Au** 196.96655	80 **Hg** 200.59	81 **Tl** 204.3833	82 **Pb** 207.2	83 **Bi** 208.98038	84 **Po** [208.98]	85 **At** [209.99]	86 **Rn** [222.02]
7	87 **Fr** [223.02]	88 **Ra** [226.03]	103 **Lr** [262.11]	104 **Rf** [261.11]	105 **Db** [262.11]	106 **Sg** [266.12]	107 **Bh** [264.12]	108 **Hs** [269.13]	109 **Mt** [268.14]	110 **Ds** [271.15]	111 **Rg** [272.15]	112 **Cn** [277]	113 [284]	114 **Fl** [289]	115 [288]	116 **Lv** [293]	117 [293]	118 [294]

Series														
*Lanthanide series	57 ***La** 138.9055	58 **Ce** 140.116	59 **Pr** 140.90765	60 **Nd** 144.24	61 **Pm** [145]	62 **Sm** 150.36	63 **Eu** 151.964	64 **Gd** 157.25	65 **Tb** 158.92534	66 **Dy** 162.50	67 **Ho** 164.93032	68 **Er** 167.259	69 **Tm** 168.93421	70 **Yb** 173.04
†Actinide series	89 **†Ac** [227.03]	90 **Th** 232.0381	91 **Pa** 231.03588	92 **U** 238.02891	93 **Np** [237.05]	94 **Pu** [244.06]	95 **Am** [243.06]	96 **Cm** [247.07]	97 **Bk** [247.07]	98 **Cf** [251.08]	99 **Es** [252.08]	100 **Fm** [257.10]	101 **Md** [258.10]	102 **No** [259.10]

[a] The labels on top (1A, 2A, etc.) are common American usage. The labels below these (1, 2, etc.) are those recommended by the International Union of Pure and Applied Chemistry.

The names for elements 113, 115, 117, and 118 have not yet been decided.

Atomic weights in brackets are the masses of the longest-lived or most important isotope of radioactive elements.